U.S. EPA BOARD OF SCIENTIFIC COUNSELORS
Endocrine Disrupting Chemicals Subcommittee

Face-to-Face Meeting Summary
Research Triangle Park, NC
December 13–15, 2004

Monday, December 13, 2004

Welcome and Opening Remarks

Dr. Anna Harding welcomed participants to the meeting of the Endocrine Disrupting Chemicals (EDC) Subcommittee. She thanked Dr. Elaine Francis and her team for the excellent work in preparing the meeting materials, Dr. Larry Reiter for Office of Research and Development (ORD) support, and the many scientists within the Agency who have contributed to the research program, organization of the meeting, and other aspects of the review process. She commented that the Subcommittee looked forward to the presentations and posters as well as the opportunity to meet with scientists in the program. She also thanked Dr. Neil Stiber for serving as the Designated Federal Officer (DFO) for the Subcommittee and Dr. James Avery, who served as the substitute DFO for Dr. Stiber during this meeting.

Dr. Harding introduced the Subcommittee members:

- ✧ Dr. George P. Daston, from the Procter & Gamble Company
- ✧ Dr. Glen R. Boyd, from the Department of Civil and Environmental Engineering at Tulane University
- ✧ Dr. George W. Lucier, formerly with the National Institute of Environmental Health Sciences (NIEHS)
- ✧ Dr. Stephen H. Safe, from Texas A&M University
- ✧ Dr. Juarine Stewart, from the School of Computer, Mathematical and Natural Sciences at Morgan State University
- ✧ Dr. Donald E. Tillitt, from the U.S. Department of the Interior, U.S. Geological Survey
- ✧ Dr. Glen Van Der Kraak, from the University of Guelph
- ✧ Dr. Anna Harding, from Oregon State University.

Dr. George Daston was unable to attend the meeting.

At the request of Dr. William Farland, the Board of Scientific Counselors (BOSC) Executive Committee decided in May of 2004 to conduct pilot program reviews for ORD's Endocrine Disruptors and Global Change Research Programs. The pilot program reviews differ from previous Multi-Year Plan (MYP) reviews because they feature retrospective as well as prospective evaluation, examining current progress and the future direction of EPA research in this program. The review is meant to provide guidance to help ORD strengthen areas such as research accountability, communicate about research progress and results, and incorporate information that responds to the growing emphasis on evaluating federal research. The EDC Subcommittee is the first subcommittee to perform an evaluation of this sort, and the results of this review will guide future BOSC program reviews.

In fall 2004, the BOSC formed the EDC Subcommittee, developed and approved charge questions, and asked the Subcommittee to begin the review process. The EDC Subcommittee will provide to the BOSC Executive Committee a written report following the January meeting (draft report). The objective of the EDC program review is to provide independent review regarding the relevance, quality, performance, scientific leadership, and resources of the program. The Subcommittee's approach to the review is to respond to a series of questions organized into five broad charge questions. The questions were framed to solicit comments on: (1) program design, (2) relevance, (3) program progress in addressing key scientific questions impacting environmental decision making, (4) leadership, and (5) resources. The review is organized around the three long-term goals (LTGs) that are presented in the program's MYP. The first three charge questions, related to program design, relevance, and program progress, will be addressed for each LTG. The last two charge questions, analyzing leadership and resources, will be evaluated separately because they cut across the entire program.

The Subcommittee had two conference calls during the past 2 months to discuss the charge questions, review background materials that were sent to them and discuss these materials with Dr. Francis, delineate writing responsibilities, and develop a draft format of the report. At this meeting, the Subcommittee members also received miniaturized copies of the posters, copies of the PowerPoint presentations, and summaries of Science To Achieve Results (STAR) reports. Most importantly, the Subcommittee members had the opportunity to hear the presentations, view the posters, and participate in question-and-answer sessions with the scientists performing this research.

The agenda for this meeting was modeled after reviews conducted at the division level by the National Health and Environmental Effects Research Laboratory (NHEERL). A series of introductory and welcome presentations was followed by a brief overview of the EDC research program, including the LTGs, presented by the National Program Director, Dr. Francis. On Day 1 of the meeting, Dr. Ralph Cooper presented an overview of LTG 3, Support for the EPA Screening and Testing Program. Next, a poster session was held at which principal investigators presented research related to this particular LTG. The poster session was followed by discussion time during which the Subcommittee members had the opportunity to have one on one discussions with the investigators. Discussion times and work sessions for the Subcommittee were allotted throughout the 3 days of the meeting. Day 2 began with presentations on LTG 1, by Drs. Earl Gray and Greg Sayles, with a poster session and discussion immediately following. After lunch Dr. Gregory Toth gave a presentation on LTG 2; this was followed by a poster session, discussion period, and work session. Day 3 started with presentations by Agency program and regional offices that use the science resulting from the research program, speaking to the relevance of the research program. These presentations were made by Dr. Joseph Merenda from the Office of Prevention, Pesticides and Toxic Substances (OPPTS) and Dr. Bobbye Smith from Region 9. Finally, Dr. Francis offered closing remarks and the Subcommittee convened to develop an oral report that served as the EDC Subcommittee's draft response to the charge questions. The Subcommittee scheduled a conference call for early January at which time it will assess progress on the report and hopefully meet the goal of producing a draft written report to present to the BOSC Executive Committee, which will meet in late January. Lastly, the agenda included a public comment period on Monday afternoon from 2:30 to 2:45 p.m.

Dr. Avery thanked Dr. Harding and the Subcommittee members for using their valuable time to participate in this review. He stated that his role as DFO for this meeting is to serve as a liaison between the Subcommittee and the Agency and ensure that the meeting complies with the rules set by the Federal Advisory Committee Act (FACA). For the benefit of the Subcommittee and

others attending the meeting, Dr. Avery provided a brief summary of some of the key points of FACA. He noted that public comments should be limited to 3 minutes for each comment; as of Monday, no requests for public comment had been received. Participants were asked to notify Dr. Avery if they would like to provide a public comment. At the end of the meeting, the Subcommittee presented a draft oral report of its findings. In closing, Dr. Avery thanked the Subcommittee members for their participation and commented that he looked forward to working with them during the course of the meeting. He noted that, following this meeting, all communications regarding ethical responsibilities should be directed to Dr. Neil Stiber, the DFO for this Subcommittee, or Ms. Lorelei Kowalski, the DFO for the Executive Committee of the BOSC.

Introduction to Endocrine Disruptors Research Program and Program Review
Dr. Lawrence W. Reiter
Director, National Health and Environmental Effects Research Laboratory

This is the first of a number of program reviews examining ORD scientific management issues that will be performed by the BOSC. This presentation provides information on the background of the EDC program and the importance of this program within the Agency and at national and international levels.

EPA began studying EDCs because there was growing evidence suggesting that exposure to environmental chemicals could cause adverse effects on the endocrine system in both human and wildlife populations. Potential EDCs include pesticides and industrial chemicals for which EPA has regulatory authority under statutes such as the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA). A research program was needed to address major scientific uncertainties in our understanding of EDC's including the nature of the effects, the extent of the problem in human and wildlife populations and the dose-response relationships for EDC exposures. The initiation of an ORD research program was spawned by a Risk Assessment Forum meeting in 1994 which introduced this topic to the Agency. Prior to this time, federally-funded research in this area was limited, a notable exception being the program at NIEHS on environmental estrogens. The importance of this program to EPA markedly increased by passage of the FQPA and SDWA in 1996 which required EPA to develop a program to screen and test for EDC's. In 1999, Dr. Elaine Francis was named as National Program Manager of the Endocrine Disruptors Research Program, indicating the high profile and importance of the program to the EPA. The Program designs and tracks research addressing the major uncertainties noted above.

Within EPA, the Endocrine Disruptors Research Program develops methods for implementation of the Endocrine Disruptors Screening Program (EDSP) and prioritizes chemicals for EDSP in conjunction with the Computational Toxicology Research Program. These methods will be used by regions and states, incorporated into large-scale ecological and human studies, and used for risk management activities. The program also strives to improve the underlying science informing EPA risk assessments and decisions; determines the impact of environmental exposure on humans, wildlife, and the environment; and provides information on specific chemicals. Nationally, the Program took a leadership role in supporting the Committee on Environment and Natural Resources (CENR) Endocrine Disruptors Interagency Working Group, which documented research needs, developed a federal inventory of government-sponsored EDC research; activities used to developed a set of national research priorities. Internationally, members of the Endocrine Disruptors Research Program have participated in the annual G-8 Environmental Ministers Meeting, helped to develop a Global Endocrine Disruptors Research

Inventory and a "Global State-of-the-Science" report to the World Health Organization, and assisted with organizing workshops with Organization for Economic Cooperation and Development (OECD) work groups.

From EPA's perspective, the goals of the BOSC Subcommittee Program Review are to evaluate the program's design, relevance, progress, leadership, and resources. The evaluation and recommendations arising from this review will help ORD plan, implement, and strengthen the program; make future research investments; and prepare performance and accountability reports for interaction with the Office of Management and Budget (OMB). Concerning program design, the Subcommittee will evaluate goals and priorities of the research and MYP and provide feedback concerning the role that the program fills in sponsoring research relevant to EPA needs and coordinating collaboration with other agencies and participants in the research enterprise. Evaluation of program relevance will assess whether: the research is driven by EPA priorities, program and regional scientists are included in setting priorities, and the research has an impact on EPA decision-making. The efficiency of transferring information to clients within EPA also will be assessed. Evaluation of program progress will consider the soundness of research approaches, advancement of scientific understanding, and the impact of research results on scientific decision-making. Leadership issues will include assessing the degree to which both the program and scientists within the program are considered to be at the forefront of EDC research. Evaluation of program resources will focus on the appropriateness of the current level of program funding (approximately $12 million) and whether resources are allocated effectively.

National Program Director's Welcome: ORD's EDC Research Program

Dr. Elaine Francis, National Program Director for the Endocrine Disruptors Research Program National Center for Environmental Research

EPA's ORD is composed of three National Laboratories and four Centers. Two of the Centers were created recently—the National Homeland Security Research Center and the National Computational Toxicology Research Center. ORD balances problem-driven research designed to address EPA's mission with basic or core research projects, selected on the basis of their broad applicability, relevance to EPA, and scientific merit. The EDC program encompasses both of these research functions, with core research designed to elucidate pathways of EDC toxicity; development of methods, models, and measures of EDC activity; and application of these methods, models, and measures to determine the impact of EDCs. The ORD research planning process is based on input from the EPA Strategic Plan, ORD strategic planning, customer/user needs (i.e., EPA program offices and regions including OPPTS, and federal research partners), and outside peer advice from groups such as the Science Advisory Board (SAB), BOSC, and National Research Council (NRC). ORD's overall goal is to provide the best available science to support the protection of public health and safeguard the environment.

Funding for EDC research for the years 1998-2005 has ranged from a low of $8 million to a high of $12.6 million. The extramural grants program, Science to Achieve Results (STAR) averages $4 million annually, although only $2.7 million was received for 2004, and funding is uncertain for 2005, as it was eliminated in the President's Budget. The STAR program represents an important source of extramural expertise for the EDC program. Ideas for Requests for Applications (RFAs) come from program offices, regions, and ORD laboratories; proposals received in response to an RFA undergo external peer review before they are sent to internal programmatic review teams for further scrutiny. Proposals are recommended based on relevancy to EPA's mission, balance of the research portfolio, and the extent to which they supplement in-

house research. The current portfolio includes 40 grants covering a broad array of toxics, species, and chemicals; an upcoming RFA will focus on exposure issues.

The EDC Research Program covers a diverse range of topics ultimately designed to determine the effects of EDCs on human and ecological health. Research approaches include computational, laboratory, and field studies, ranging from molecular to whole organism research encompassing invertebrates to humans, and includes biological, analytical, and engineering expertise. The Multi-Year Plan (MYP) for the EDCs research program delineates three Long Term Goals (LTGs):

- ✧ Provide a better understanding of the science underlying effects, exposure, assessment, and management of endocrine disruptors. Key issues include examining dose-response relationships, developing needed extrapolation tools, determining the effects of multiple EDCs, managing unreasonable risk, and developing risk assessment approaches.

- ✧ Determine the extent of the impact of endocrine disruptors on humans, wildlife, and the environment. Key topics include determining exposure, identifying responsible chemical classes, identifying major sources and fates, and determining effects on human and wildlife populations.

- ✧ Support the Agency's screening and testing program through development of screens and tests to support EPA's mission and provide assistance in standardization and validation of these tests.

EDC research activities lead to outputs such as improved protocols for screening and testing EDCs and risk management tools and approaches that can be transferred to customers including EPA program offices, regions, and other federal and international organizations. Short-term outcomes of this knowledge transfer include development of standardized screening and testing protocols, determination of source of exposure to EDCs and efficacy of risk management approaches, and improved knowledge concerning the extent to which EDCs contribute to adverse human or ecological health outcomes. The desired long-term outcome of the program includes the reduction or prevention of risk to humans and wildlife from EDC exposure.

The Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) was chartered on October 16, 1998, to address development and implementation of the Agency's Endocrine Disruptors Screening Program (EDSP), as mandated by the Food Quality Protection Act and Safe Drinking Water Act Amendments of 1996. Key recommendations arising from this Committee included recommendations to examine estrogenic, androgenic, and thyroidogenic effects of EDCs; examine ecological effects as well as human health; and expand the focus to a broad range of chemicals and not just those found in and on food and in sources of drinking water. EDSTAC charged the program with developing Tier 1 screens to detect the potential of a chemical to interact with the endocrine system and Tier 2 tests including multi-generational studies covering a broad range of taxa providing data for hazard assessment. ORD research develops these screens and tests, which then are passed to the Office of Science Coordination and Policy (OSCP) for validation and implementation in EDSP.

The progress that has been made in the EDCs research program can be ascertained by reading the MYP , the NHEERL research implementation plan, by the bibliography of nearly 400 articles published in peer reviewed journals (111 for LTG 1, 216 for LTG 2, and 67 for LTG 3), through the poster abstracts and presentations, STAR project summaries, and workshop proceedings.

Previous peer reviews have examined components of the program, including the research plan, a number of division-level reviews, research used for regulatory decisions, and the STAR program by the National Academy of Sciences. Program scientists have served in many leadership capacities including as officers in professional societies; on national and international workgroups; on publication boards; and as invited speakers, session chairs, and organizers of scientific meetings. Program scientists also have received honors including Best Poster at the Gordon Conference; Best Paper of the Year in Toxicological Science; EPA Bronze, Silver, and Gold Medals; ORD Team Awards; and OPPTS Awards. The program also is actively training future researchers, with 51 current and 53 former postdoctoral and predoctoral fellows. In addition, the program provides advice to EPA for development of Integrated Risk Information System (IRIS) documents, risk assessments for perchlorate and dioxin, and the Computational Toxicology Research Framework.

EPA's EDC research program is leading national and international efforts to address global concerns regarding exposure to environmental agents that interfere with the endocrine system and provides the scientific basis for developing assays for screening and testing programs. The Agency's long-term research on EDCs will help to determine whether humans and wildlife are impacted by EDCs in the environment, identify sources of exposure, and develop approaches to reduce or prevent future exposures.

Questions for Dr. Francis

Dr. Lucier asked about accounting for the contribution of funds for RFAs issued jointly with NIEHS. Dr. Francis answered that contributions from EPA and NIEHS are counted separately. For a recent joint RFA for epidemiological studies, EPA contributed $10 million, while NIEHS, National Cancer Institute (NCI), and National Institute for Occupational Safety and Health (NIOSH) contributed $9 million; this $9 million is not counted as part of the EPA funding pool. For these jointly issued RFAs, agencies take the highest ranked proposals and decide which to fund, and then NCI focuses on issues related to cancer, for example, while NIOSH might focus on worker exposures. EPA tends to fund proposals to study emerging chemicals while NIEHS focuses on "classical" chemicals. Dr. Lucier mentioned collaborations with the U.S. Geological Survey (USGS) to measure EDC levels in waterways, and asked whether there was a corresponding collaboration with the Centers for Disease Control and Prevention (CDC) to measure EDC levels in urine, for example. Dr. Francis responded that EPA researchers are serving on CDC work groups to identify and prioritize monitoring of chemicals of interest.

Dr. Lucier commented that defining an EDC appears to be an ongoing issue, and this program seems to use a broader definition. Dr. Francis replied that the program uses the International Programme on Chemical Safety (IPCS) definition. Dr. Lucier asked whether this broadening of work outlined by EDSTAC was causing any problems. Dr. Francis responded that the program offices ultimately would determine which chemicals would be classified as EDCs, and that working on suspected EDCs was not problematic.

Dr. Stewart asked whether the Agency tracks predoctoral and postdoctoral fellows after they leave EPA. Dr. Francis explained that there is no formal tracking system, but EPA has informal information concerning the initial positions fellows take after leaving the Agency; there is, however, little information on subsequent positions.

Dr. Harding commented that EPA had not fully funded the EDC program in the last few years, and asked about EDC efforts in other agencies. Dr. Francis noted that other agencies do not have

integrated EDC programs; their research efforts are more scattered. For example, USGS measures suspected EDC activity, but this is not part of a formal EDC program.

Dr. Boyd asked about funding for the STAR program for 2005. Dr. Francis answered that at its highest level, STAR program funding for EDCs was approximately $5 million. This amount decreased to $4.7 million in 2003 and to $2.7 million in 2004. EDC funding through the STAR program was eliminated in the President's Budget for 2005, but Congress recommended $2 million for the program. With this new appropriation, the program can continue at a reduced rate. Dr. Boyd asked whether STAR program funding was critical to continuation of the EDC program, and whether loss of funding would affect progress. Dr. Francis emphasized that STAR program funding is critical to help understand the effects of exposure to EDCs. A series of exposure-related RFAs had been planned to complement intramural research. She hopes to be able to issue the RFAs and after the research is underway, convert them to cooperative agreements. Dr. Stewart asked about the effects of reduced STAR program funds on ongoing EDC grants. Dr. Francis responded that the program forward-funds grants so that recipients receive 3 years of funding when they are awarded the grant to avoid halting ongoing research; as a result, fewer proposals received in response to an RFA are funded.

Dr. Safe asked whether research was underway to integrate foods that have endocrine effects with the effects of EDCs on human health. Dr. Francis replied that interagency working groups discussed joint projects to examine phytoestrogens, pharmaceutical, and nutraceuticals. One project under the STAR program that examined phytoestrogens was funded.

LTG 3 Presentation: Research Supporting the Agency's EDC Screening and Testing Program

Dr. Ralph L. Cooper
National Health and Environmental Effects Research Laboratory

ORD supports "problem-driven" research, conducted to aid EPA in implementing its congressionally mandated EDSP. ORD develops protocols and provides scientific expertise for transfer and validation of protocols that EPA will use in mandated screening and testing programs. The ORD has a history of research aimed at measuring the effects of environmental chemicals through development of both Tier 1 screens and Tier 2 tests. ORD's history of identifying and evaluating EDCs predates both the FQPA and SDWA. ORD focuses on implementation of screens and tests as required by EDSTAC. The EDSP framework includes efforts in priority setting, screening, and testing. Screening identifies substances for further testing, while testing identifies adverse effects and establishes dose-response relationships for hazard testing. This also includes multigenerational studies covering a broad range of taxa.

The 15 posters presented for LTG 3 were categorized to address priority setting, Tier 1 screens, or Tier 2 tests. Priority setting included posters on molecular modeling. Tier 1 screens identify substances for further testing, based on their impact on estrogen, androgen, or thyroid hormone pathways, or on the hypothalamic-pituitary-gonadal axis, and include screens for estrogen receptor (ER) or androgen receptor (AR) binding, steroidogenesis, the Hershberger assay to detect androgenic or anti-androgenic activity, and a fish reproduction screen, among others. Tier 2 tests characterize the nature, likelihood, and dose-response relationship of EDCs in humans and wildlife, and include studies examining mammalian, fish, and avian two-generation reproductive studies. In addition to posters describing research efforts pertaining to LTG 3, Dr. Gary Timm presented a poster featuring OSCP's perspective on ORD's role in the EDSP, examining how researchers in ORD have helped OSCP develop, standardize, and validate

protocols. Dr. Kavlock also presented a poster describing the role of computational approaches for improving priority setting and the screening and testing of potential EDCs. In the future, research will focus on ways to develop an *in vitro* battery of tests to quickly screen chemicals for EDC activity to help reduce the reliance on animals for testing. Information on EDC modes of action will be useful for developing these *in vitro* methods.

Working Lunch

Subcommittee members met for a working lunch session starting at 12:30 p.m. Dr. Stiber, who participated by telephone, thanked the Subcommittee members for their participation in reviewing EPA's Endocrine Disruptors Research Program and thanked Dr. Avery for serving as DFO in his absence. Dr. Harding asked the Subcommittee members to discuss the organization and scheduling of discussions and writing tasks, given the time constraints set by the agenda, so that an oral report could be presented on Day 3 of the meeting (i.e., December 15). Dr. Avery cautioned that FACA rules would apply when more than one-half of the Subcommittee meets, but that FACA rules would not apply to the working groups.

Dr. Harding suggested that each working group develop a draft report on its assigned LTG and select one individual to serve as a spokesperson to present the individual sections on Day 3. Dr. Lucier cautioned that the entire Subcommittee should discuss the various sections to ensure that they do not contradict each other in the final report.

Subcommittee members agreed that they would fully discuss LTG 3 and some of the other goals on Day 1 of the meeting because there was less time for discussion on subsequent meeting days. Dr. Harding asked the Subcommittee members to submit the drafts of their sections of the report to her by the end of the meeting so that she can incorporate their comments into the final written report that will be presented to the BOSC Executive Committee.

Dr. Safe asked about the level of detail required in the report. During the conference call held on December 1, 2004 (Dr. Safe did not participate), members discussed the 2003 external peer review report on NHEERL's Experimental Toxicology Division (Chaired by Dr. I. Glenn Sipes of the University of Arizona) that provided information on the level of detail needed and the approximate length of the report. The report must be useful and meaningful for the review. Dr. Stewart commented that perhaps discussion of problem-free program areas could be shortened to leave space for comments about less successful program areas. Dr. Lucier observed that the report should include a concise summary of the positive aspects of the program in terms of relevance, initial planning, amount of progress, etc.; individual projects, however, need not be described in detail. Dr. Tillitt commented that OMB will want to know if the program is addressing and meeting its goals; this assessment should be included in the report so that the Subcommittee can inform the EDC Program Director about the need to enhance their activities or redirect their efforts or resources.

Dr. Boyd stated that his working group was developing a brief description of the program, including program goals and specific objectives. He thought that it would be useful for individuals in EPA who are engaged in the program, such as Dr. Francis, to provide some feedback and ensure that Subcommittee members had access to the most recent information. Dr. Avery pointed out that Dr. Francis could answer the Subcommittee members' questions, and that materials provided could be updated and clarified. He added that the BOSC Executive Committee is seeking advice from Subcommittee members and that the report would be presented to the Executive Committee, not to EPA. The Executive Committee will review the

report, make suggestions for revisions, approve the final report, and submit it to EPA. Dr. Lucier expressed some concern about allowing EDC program staff to review preliminary drafts of the report. This review was intended to be an independent peer review, and allowing program staff to review a draft might compromise the peer review process.

Subcommittee members discussed the organization of the written report. Dr. Harding asked members if they had received a template of the report, which she e-mailed to them on December 10, 2004. That template began with an executive summary and discusses each goal, with charge questions included as subcategories under each goal. Dr. Tillitt asked whether each LTG would include a discussion of key issues/areas using the same format, or whether information from each of the key issues/areas would be blended into one structure. Dr. Harding and other Subcommittee members agreed that the information should be blended. Dr. Lucier commented that the section on LTG 2 will need to be organized to capture EDC effects on both wildlife and human health.

Dr. Van Der Kraak clarified that rather than focusing specifically on program design and then discussing it in relation to each individual task, program design will be discussed in a generic sense under a given LTG, not separated into intricate parts. He suggested that the report include a matrix in which approaches are checked off (i.e., screening assays, testing assays, computational toxicology approaches), but he asked whether these issues all should be discussed in one statement on program design. Dr. Harding confirmed that issues should be discussed together because the Subcommittee does not have time to develop a very detailed report. Dr. Lucier agreed, but stipulated that Subcommittee members still should examine the individual components carefully to ensure that nothing is omitted.

Dr. Lucier asked for clarification on the report template. Specifically, he asked whether the strengths, weaknesses, and challenges addressed in the first part of the report, followed by a description of the LTGs, constituted the review of each LTG or was simply a summary of the entire report. Dr. Harding explained that the report would begin with an executive summary, followed by more detailed reviews of the LTGs. Approximately 4 pages should be devoted to the discussion of each goal. She asked the Subcommittee members to include what they think is important but to try to keep the writing concise. The Subcommittee then discussed working plans for the remainder of the meeting.

Dr. Harding commented that nearly all of the goals set forth under LTG 3 have been achieved. Dr. Van Der Kraak noted that some goals were overly ambitious; the program did not quite achieve what it set out to accomplish 2 or 3 years ago, probably because of unrealistic goals and objectives. Refocusing by the Program Director has resulted in a more realistic timeline. Dr. Lucier added that some of the timelines had been legislatively mandated.

Dr. Van Der Kraak raised the issue of challenges faced by the program. One challenge relates to whether it is possible and advisable to fully develop all the various test methods currently available, or whether it is necessary to establish a prioritization process for optimizing use of resources in this endeavor. Dr. Lucier commented that they would need to set priorities for validation of test methods. Dr. Van Der Kraak stated that the challenge is for the program to effectively use its resources and strategically select tests for full development and validation. Dr. Harding added that the lack of resources is a challenge for the program, especially because it seems clear that funding for the STAR program will likely decline, in addition to other funding cuts and hiring freezes.

Concerning the EDC program budget, Dr. Lucier commented that he is not sure how the actual dollars are counted and thought that expenditures probably were underestimated. Nonetheless, the program has been very successful with the available funds. He asked about money from other sources, such as the Computational Toxicology Program, and stated that he does not know how the program counts facilities and other factors that determine the budget. The program probably spent more than the $12 million stated as its budget. Dr. Francis explained how the budget for the program was determined. The cost of a full-time equivalent (FTE), which includes salary, travel, and infrastructure, was set at $123,000 per FTE. The program currently has about 55 FTEs, costing approximately $6.5 million. Dr. Stewart asked how this money was allocated across the LTGs and whether it included costs for items such as personnel, new equipment purchases, and maintenance of old equipment. Dr. Francis did not have that level of detail because those issues are decided on a laboratory-specific basis. She noted that this topic was discussed in the meeting materials distributed to the Subcommittee; Dr. Francis offered to obtain any additional information on budget needed by Subcommittee members. Dr. Stewart requested information that discusses budget details across the ORD centers and laboratories.

Dr. Van Der Kraak asked for clarification of how the $12 million was spent. If $6.5 million was required to fund the 55 FTEs and $4 million was used to fund STAR grants, only $1.5 million remains for research. Dr. Francis answered that of the $12 million total budget, approximately $5 million was used to fund grants, and the remaining $7 million pays for a combination of items such as salaries, infrastructure, travel, and new equipment. She clarified that the FTE unit cost of $123,000 includes research costs in addition to salary and benefits. Dr. Harding asked if the scientists working on EDC research work simultaneously on other research tasks. Dr. Francis said this was the case, and that 1 FTE could work on, for example, as many as three tasks, resulting in 0.33 FTEs per research task. Dr. Lucier added that 55 FTEs could encompass 155 people. Dr. Francis confirmed this and added that the FTE assessment included support staff as well as investigators; postdoctoral fellows were counted separately. Dr. Stewart asked whether technicians were paid through contracts or by EPA. Dr. Francis answered that the technicians were paid by EPA.

Dr. Harding adjourned the working lunch session at 1:30 p.m.

Discussion Session: LTG 3

Dr. Harding opened the LTG 3 discussion session and called for comments from the Subcommittee members.

Dr. Safe commented that the posters presented for LTG 3 showed excellent progress in development of *in vitro* assays for endocrine disruptors, with some of the assays available from American Type Culture Collection. All of the assays are standardized fairly well and more than one assay exists for some steroids (e.g., AR and ER assay), while others (e.g., thyroid hormone), represent more complicated systems for which the assays are not as advanced. This part of the program has accomplished its goals and the scientists involved in this research now should be able to move on to other projects.

Dr. Van Der Kraak noted that EPA has been very responsive to criticisms of some mammalian *in vivo* test methodologies. For example, questions arose concerning the effects of changes in feeding or body weight gain on some of these assays, and EPA performed experiments and evaluations to address these concerns. Excellent progress has been made in the area of wildlife assays, including the development of the amphibian thyroid test, 21-day fathead minnow test,

and a test developed for mycids; many of these are developed and validated to the point of being ready for transfer. Extensive progress also has been made in developing a method for examining growth and developmental effects using *Xenopus tropicalis* and through an extramural program using copepods. Good preliminary progress has been made in attempting to prioritize chemicals for testing using computational approaches. Dr. Van Der Kraak complimented the proactive approach to this issue taken by the program. He agreed with Dr. Safe that it is time for the program to consider the next generation of assays.

Dr. Safe commented that a challenge for this program, particularly for the *in vivo* assays, will be to include more relevant chemicals and putative EDCs to determine whether the assays will work for a wider range of compounds. Some assays may not work for all EDCs; for example, an assay involving copepods in sediment did not work well for polycyclic aromatic hydrocarbons because the sediments can adsorb the chemical. It will be important to understand the limitations of some of these assays, particularly as a larger variety of chemicals require testing. Dr. Lucier agreed with Dr. Safe's comments regarding selection of chemicals. Assays must be developed using well-characterized chemicals, but thought should be given to including a wider array of substances. A systematic analysis of the chemicals submitted by industry to the High Production Volume (HPV) database might be a place to start selecting less characterized chemicals to screen for potential endocrine-disrupting activity. The database provides information concerning environmental releases and whether the chemicals are present in air or water; this information might help to systematically select chemicals to test in the assays.

Dr. Lucier asked about EPA's view on using "omics" technologies ("omics" technologies includes genomics, metabolomics, and proteomics) for assay development. Dr. Kavlock commented that EPA has begun to use these technologies to develop new assays, but they are at very early stages of development. These assays are "second generation" assays not specified by the EDSTAC recommendations. Dr. Lucier complimented EPA's proactive approach to these new technologies, and asked if EPA may in the future develop an "estrogen chip" or "thyroid chip." Dr. Kavlock replied that target array chips are in the realm of possibility, especially because the costs associated with this technology are decreasing. Dr. Toth commented that crosstalk occurs between goals, particularly between groups performing core scientific research addressing the use of "omics" technology. For example, a project funded by the Computational Toxicology Program presented at the LTG 1 poster session addressed early "omics" changes occurring in the Tier 1 fish assay.

Dr. Smith commented that she participates in an internal work group to assess how the availability of new technology may be of use to EPA in terms of the Agency's congressionally mandated activities. This group was charged by EPA's Science Policy Council to ask questions on this matter internally and solicit external information as well. Dr. Lucier asked how new technologies might be used by EPA to further research in this field and extend beyond the original EDSTAC recommendations. Dr. Smith explained that there are working groups that address the use of various "omics" technologies (e.g., in decision-making activities). Program managers will provide input on specific applications for new technologies, but working groups address concerns such as the sort of chip format that would be most useful for EPA's needs; the data quality, storage, and management needs associated with new technologies; and the types of training and resources needed.

Dr. Harding asked about the involvement of regional staff in the EDC program. Do they serve on panels that make screening and testing recommendations? Dr. Smith noted that regional staff have been involved in some of the planning processes focused on pesticides, and have been

represented on the planning teams for all of ORD's goals. Some have served in designated positions (Lead Region Coordinators), and others are interested scientists who participate in the goals. With respect to the EDC program, a Regional Science Liaison to ORD from Region 5 was involved in determining a connection between pesticides and EDC research. This issue also was addressed in Dr. Smith's presentation on Day 3 of the meeting. Dr. Francis added that a representative from Region 2, who had an interest in polychlorinated biphenyl (PCB) contamination along the Hudson River, served on the EDC Planning Committee, as did a representative from Region 5 who was interested in alkyl phenols. Additionally, a regional representative from NHEERL serves on the Planning Committee.

Dr. Stewart asked if EDC program research was added to the current workload of scientists. If so, were they given additional resources to compensate for the extra work? Dr. Kevin Crofton explained that, in general, scientists slowly take on work for the EDC program because their expertise in certain areas is needed. At first, participation may simply involve attending meetings or providing advice, but their involvement gradually increases to a more time-consuming effort. To cope with these added tasks, some research projects are dropped, although additional resources can be obtained. Dr. Stewart asked whether congressional interest or a national disaster, for example, forces a change in research focus. Dr. Kavlock replied that, in this case, program office needs force the change in focus, but some chemicals may become important to a client office, prompting a shift in research priorities.

Dr. Stewart asked how additional personnel with new skills are added to the program. Dr. Kavlock replied that the number of FTEs within NHEERL has declined during the past few years; as personnel leave, they are not replaced. This slows the research and, in some cases, decreases the amount of work that can be accomplished. He explained that ORD is given an FTE ceiling by EPA management, and the laboratories and centers, in turn, are given FTE ceilings. Laboratories and centers manage their FTE needs by discussions between Associate Directors and Division Directors concerning scientific needs and strategic workforce planning. An example of this planning process concerns the area of genomics research; a commitment has been made to build capabilities in this area, so ORD is attempting to hire individuals with skills in genomics. Overall, however, reducing the FTE ceiling reduces the ability of the Agency to undertake new areas of research, because in-house expertise in new fields is limited.

Dr. Stewart asked about mechanisms for hiring postdoctoral fellows and whether these positions were affected by the hiring freeze. Dr. Kavlock indicated that EPA uses the federal postdoctoral fellows program to hire new fellows, and it is not affected by the FTE ceiling. EPA also has other mechanisms such as training cooperative agreements with universities, including the University of North Carolina, North Carolina Central University, and North Carolina State University. Postdoctoral fellows also can be hired through arrangements with the NRC.

Dr. Lucier asked about the impact of budgetary constraints on accomplishments for LTG 3. Dr. Francis explained that LTG 3 is largely an intramural program and has not been able to grow because of the budget cuts. Despite budget constraints, the program has been able to meet deadlines demanded by the regulatory agencies, but with additional resources these deadlines could have been met more quickly and the program could have been working on next-generation technologies. Some of EDSTAC's recommendations also have hindered the program because they were not useful for accomplishing the program's research goals. Additionally, questions arise in the course of developing assays, such as the impact of body weight, route of exposure, or strain differences on the assays, and resources must be expended to address these questions. A participant commented that one issue of increasing importance to the program will be the ability

to predict the activity of compounds. Implementing Tier 1 and Tier 2 testing for every pesticide and contaminant in drinking water is not feasible; prioritization will be needed. The Computational Toxicology Program is developing some potentially useful approaches, and more funding would allow further, or faster, progress in this area. Dr. Francis added that EDSTAC thought that informed decisions concerning priority setting could be made using quantitative structure-activity relationships (QSARs), but those available at the time were not suitable for this use. This necessitated development of new approaches, perhaps computational or high-throughput screening, by the program. These approaches still are under development, so OPPTS currently uses an exposure-based method to identify chemicals to test. Dr. Gary Timm explained this method, which involves analysis of four databases of pesticide measures such as occurrence in water, occupational exposure, or occurrence in food. The first 50-100 chemicals to go through the screening program will be selected using this approach, without any consideration of their endocrine-disrupting potential. In the future, the program expects to have tools to help assess the hazard component. Dr. Boyd agreed that some of the computational methods under development will be very useful, powerful tools that can be applied to risk management.

Dr. Harding thanked the Subcommittee members and others for their participation and adjourned the session.

Afternoon Work Session

Dr. Harding explained that the Subcommittee members first would discuss LTG 3 and after the discussion break into working groups to address their respective sections of the report.

Dr. Boyd asked about criteria and methods for prioritization of compounds that will be put through the EDSP. He asked how new, potentially endocrine-disrupting compounds would be identified and prioritized for screening. Dr. Francis replied that the first round of chemicals will be selected using an exposure-based approach. The program office will implement the screening and testing program, which might identify compounds that warrant further investigation. Periodically, the program is made aware of a concern about a given chemical, particularly through the Office of Pesticide Programs, which receives data sets for pesticides that require registration. These data indicate whether there is endocrine activity for the pesticides. The program office may ask ORD to gather more information on these pesticides (e.g., determining mechanisms of action or characterizing dose response). Dr. Cooper commented that the EDC screening and testing program will have a method of prioritizing chemicals going into the screen, although the exact method is not yet established. An exercise is underway to use different computational models to validate chemical choices, using structure instead of exposure data to determine if a chemical or group of chemicals has a high probability of testing positive for endocrine-disrupting activity.

Dr. Tillitt asked whether the screening and testing program would be part of the EDC program. Dr. Francis noted that it would be separate from ORD's program. The EDC program develops methods that the program office will validate and submit for peer review; not all of the assays presented during this meeting will be part of the screening battery. After the assays have been selected, 50-100 chemicals will be tested. Pesticide registrants, manufacturers, and importers will be responsible for conducting the testing. Once the chemicals have been tested, the data will be supplied to EPA and the program office to review and use for decision-making. She noted that the presentations on the research performed under LTG 1 addressed tools for interpreting the data. Dr. Cooper added that it is ORD's responsibility to develop and standardize the assays. Once a standard protocol is developed, it is transferred to OSCP, which further standardizes and

prevalidates the protocol. ORD continues to serve as a technical consultant, but OSCP drives the prevalidation process and is responsible for completing the review, final validation, and final selection of protocols for the Tier 1 screen.

Dr. Timm explained that ORD supplies the initial protocol, which may have been developed in ORD laboratories or based on a similar assay described in the literature. OSCP takes the assay through optimization and an initial demonstration of transferability to another laboratory. In the prevalidation stage, issues often arise that are better addressed at the research laboratories rather than in the contract laboratories (contract laboratories are used because EPA does not have enough in-house resources for these activities and the assays will ultimately be performed by contractors). Consulting by ORD can involve simply passing on information from previous experience with the assay or conduct of laboratory experiments. An advisory committee provides guidance to OSCP and, in some cases, discovers additional issues that need to be addressed.

Dr. Stewart asked if there was a mechanism for obtaining assistance from a particular ORD researcher outside of the EDC program. Dr. Francis responded that if she is made aware that OPPTS needs assistance with a fish thyroid assay, for example, she speaks to her counterpart at that researcher's laboratory and requests the researcher's assistance. In some cases, it is possible to obtain assistance easily without shifting research priorities, but in other cases it may take longer to negotiate this assistance. OPPTS receives appropriations from Congress that support the contract effort component of the screening and testing program, so this type of support also is available. Postdoctoral fellows also can be brought in to do the work. Dr. Stewart asked Dr. Francis to comment on the relationship between the National Program Directors and the Laboratory Directors. Dr. Francis replied that, in most cases, she speaks initially with the Division Director; if there are problems obtaining the need support or in resolving an issue, she would elevate her request to the Laboratory Director. In response to a question concerning her position in the EPA hierarchy, Dr. Francis answered that her current position is lower than that of the new National Program Directors and different than the role described at the most recent BOSC presentation. The new National Program Directors will be on the same level as the Laboratory Directors.

Dr. Harding concluded the discussion and the Subcommittee members adjourned to different rooms for the working group sessions. The entire Subcommittee reconvened at 5:00 p.m. that day to discuss their progress.

Subcommittee Discussion of Progress

The Subcommittee met to discuss progress made on the different sections of the report. Dr. Harding asked if there were any issues or difficulties members wished to discuss, or any need for further information. Dr. Van Der Kraak stated that his group wrote a general report, which commented on the positive aspects of the program, the scope of the research, leadership issues, and challenges and recommendations; and provided general answers to the charge questions. He added that the program has made remarkable progress in spite of rather limited resources. Dr. Safe asked whether the challenges and recommendations should be listed separately or integrated into the narrative of the report. Dr. Harding indicated that challenges should be integrated, but a separate list of challenges and recommendations may be generated later.

Dr. Lucier discussed his impression of LTG 3, which changed after he saw the posters and heard the presentations. He noted that, in general, more progress has been made in ecological and

wildlife health than in human health. For key questions concerning how and to what degree human and wildlife populations are exposed to EDCs, more information is available for wildlife than for humans. Projects examining effluents from wastewater treatment plants and pulp mills might be relevant to human exposure. There is a need for a systematic evaluation of some of the major pharmaceutical classes that are released and their potential for release in wastewater. There is some ongoing interaction with CDC concerning human health issues, but there needs to be more information concerning connections between EPA, CDC, NIEHS, Food and Drug Administration (FDA), and other agencies. Dr. Safe commented that because pharmaceuticals technically could be classified as endocrine disruptors, a more specific definition of the term "endocrine disrupting chemical" is needed. Dr. Lucier commented that his main concern was systematically evaluating whether major pharmaceutical classes are escaping wastewater treatment, and if so, whether they are potential endocrine disruptors.

Dr. Lucier commented that for LTG 1, he could not easily identify projects related to issues of uncertainty for risk assessment. Issues such as additivity, cumulative risk, children's risk, and genetic variation were not fully explored in the research described for this goal. EPA may intend to rely on the National Center for Toxicogenomic Research or the National Institutes of Health (NIH) to generate this information, rather than performing the research itself. Nonetheless, individual variation will be an important part of risk assessment.

Dr. Boyd asked how analytical methods are integrated into overall risk management. A stumbling block may be whether EPA relies on other organizations or funding sources to develop these methods. He also commented on program progress, identifying a goal to analyze EDCs in sediments that had not yet been addressed, although it was part of the annual performance goals for 2004. Dr. Tillitt commented that EPA has made significant progress in endocrine-related research that is not reflected in the report (e.g., dioxin-related research is not included because dioxin is not categorized as an EDC). Dr. Francis explained that research on dioxin and PCBs is covered under EPA's Human Health MYP, not under the EDC program; the Human Health Research Program also covers research on genetic variability. Despite the obvious links between the two programs, they are funded separately. Dr. Lucier commented that it will be important to explicitly state that this research is underway in a different program because genetic polymorphisms (e.g., in steroid hormone receptors), will affect responsiveness, create individual variation, and impact risk assessment for endocrine-disrupting chemicals.

Dr. Stewart asked whether the $12 million EDC budget was a pool of money to be spent at the Program Director's discretion or constituted time and effort from different scientists at different laboratories that contribute to EDC research. Dr. Francis commented that the latter was true, except for the STAR program. Dr. Francis explained that the appropriations bill provided $2 million for the STAR program, but there is not yet an official 2005 budget. Dr. Tillitt noted that the STAR program appeared crucial for providing the EDC program with needed extramural expertise. Dr. Francis agreed and added that the academic community is very interested in the STAR program because it supports research that is not funded by other agencies or organizations. NIEHS provides support for projects related to human health, and the National Science Foundation (NSF) supports research on wildlife, but not necessarily exposure of wildlife to EDCs. Dr. Harding asked how much funding had been requested for the extramural program. Dr. Francis explained that the President makes the request and the Agency supports the President. This year, the President did not request additional dollars for the STAR program. In the past, the EDC program received up to $4.7 million. Last year, the program received only $2.7 million; this year, Congress requested $2 million, but this still leaves the program short of adequate funds.

As part of a brief discussion on wastewater treatment issues, Dr. Safe commented that almost any toxic chemical disrupts an endocrine pathway, so there is a need for selectivity in terms of which chemicals are covered under this definition. He added that in areas with large elderly populations (e.g., Florida) that take more prescription drugs, the levels of these drugs in rivers could be a significant issue. Dr. Francis commented that the screening program is beginning to screen for activity, not just for specific chemicals.

Dr. Harding concluded the discussion and adjourned Day 1 of the meeting at 5:30 p.m.

Tuesday, December 14, 2004

LTG 1: Improving Scientific Understanding: Effects Using Mammalian and Aquatic Models

Dr. L. Earl Gray, Jr.
National Health and Environmental Effects Research Laboratory

Research performed under LTG 1 is aimed at strengthening the science underlying the effects of EDCs in animals. This research addresses the ability to extrapolate the effects of EDCs across species, determining dose-response curves for EDCs, understanding mechanisms of EDC action during critical life stages (including reproduction), and determining cumulative toxicities of EDCs.

Interspecies extrapolation for the effects of EDCs is based on highly conserved components of the endocrine system at both the cellular and molecular levels, with similarities between species observed in mechanism of action, pathways, and steroidogenesis. The effects of endocrine disruptors, however, can vary greatly between species. ORD research projects seek to determine which EDC mechanisms can be extrapolated among all classes of vertebrates (and perhaps invertebrates as well). Comparative binding assays have found similar binding affinities across species for ERs and ARs. Work in this area also has identified a novel membrane-bound progesterone receptor. Other projects in this area have assessed the effects of aromatase inhibitors in fish and mammals, the effects of bromodichloromethane on rat pregnancy and human placental cell cultures, and the effects at several levels of biological organization of common chemicals across multiple species.

In vitro studies on dose response have delineated U-shaped dose-response curves for several anti-androgens. Inverted U-shaped curves are observed for several xenoestrogens including combustion byproducts and methoxychlor metabolites. Determining dose-response curves and exposure thresholds will provide important information for risk assessment activities.

Ongoing research sponsored by the EDC program also is examining the developmental effects of EDCs, which can have serious effects on differentiation systems. Effects can occur at very low dosage levels, may be more severe than effects seen in adults, and may be latent or difficult to detect until later in life. Posters presented during this session described work examining the developmental and reproductive effects of EDCs, including the effects of androgens and estrogens on the development of several fish species and rats, and posters examining the mechanism and effects of thyroid hormone system disruption, particularly on the central nervous system. Data concerning the ability of some EDCs, such as vinclozolin, methoxychlor, PCBs,

and atrazine, to disrupt reproduction and development have been incorporated into existing risk assessment strategies for these compounds. Finally, posters examining the effects of cumulative toxicity of EDCs also were included in this session and examined how mixtures of EDCs affect endocrine signaling and whether additivity accurately estimates the low dose effects of dioxins and non-dioxin-like PCBs.

LTG 1: Improving Scientific Understanding: Exposure and Risk Management Methods Development

Dr. Gregory Sayles
National Risk Management Research Laboratory

LTG 1 focuses in part on strengthening the science underlying risk management of EDCs. Dr. Sayles presented information describing how risk and risk management research are used to decrease the uncertainty of the risk management decision-making process. Two major questions underlying risk management science of EDCs are:

- ✧ What are the major sources and environmental fates of EDCs?
- ✧ How can unreasonable risks be managed?

The Risk Management Evaluation process identifies the current state of risk management science and engineering for a particular problem, in this case, EDCs. An initial list of suspect EDCs was determined using assessments of compounds with known endocrine activity (as identified in the literature and by work done under LTG 1-3) and known exposure. Incorporation of known risk management strategies along with external peer review leads to accepted risk management research questions. After the research questions have been defined, decisions must be made concerning which questions to pursue. These decisions are made based on assessment of available skills (including those available through collaborations), resources and resource leveraging, and identification of other programs within ORD that may work on these issues. Ultimately, research products are developed that can be used by clients to reduce the uncertainty of risk management decisions. Initial compound classes identified for risk management research include highly suspected EDCs such as reproductive steroid hormones, alkylphenol ethoxylates and their biodegradation products, and chlorinated dioxins and furans. Initial studies on source characterization focused on wastewater treatment plants, concentrated animal feeding operations (CAFOs), and combustion as important sources of exposure.

Wastewater treatment, in particular, is a major component of risk management research, and ORD has been able to collaborate with other programs including ORD's Water Quality and Drinking Water Research Programs, USGS, and the Water Environmental Research Foundation. Several posters presented in this session focused on determining fates and biodegradation products of EDCs resulting from wastewater treatment strategies. Other posters described source characterization from effluents and the fate of alkylphenols in land-applied biosolids. Since chemical and biological assays to monitor risk management processes are not standardized, research was required to develop assays making use of gas chromatography/mass spectrometry (GC/MS), high-performance liquid chromatography (HPLC), and an adaptation of a fish estrogenicity assay.

In addition to posters in LTG1 on wastewater treatment, drinking water treatment, pollution prevention approaches and the development of assays, Dr. Sayles described the risk management posters presented as part of LTG 2. This work includes characterization of combustion sources

through application of combustion samples to endocrine bioassays, HPLC fractionation, and GC/MS identification. Another poster characterized hormones found in swine lagoons.

EPA's risk management EDC research is unique in integrating breadth of research, intra- and inter-organization collaborations, and products for regulatory clients. The program has processes in place to identify research that focuses on the most relevant chemicals, sources, and risk management strategies, and allows refocusing as more information becomes available. Several analytical methods developed in this program are in use in risk management programs.

Discussion Session: LTG 1

Dr. Boyd opened the discussion on the posters pertaining to risk management issues, commenting that the overall approach and quantity of work is appropriate and that the research is proceeding on schedule. The program runs the risk, however, of being unable to continue without sufficient funding. Suitable approaches to identify sources of EDCs using state-of-the-art tools are in use, as are tools to predict appropriate treatment technologies and develop approaches for future risk management research. Further consideration of the state-of-the-art in terms of technologies targeted for future research, as well as justification for the future direction of the overall risk management program, should be communicated clearly. The rationale for allocating program resources and the process for deciding on which technologies and specific compounds to focus are appropriate, but not communicated as clearly as they could be. Taxpayers might wish to be better informed of the thought processes that go into evaluating the massive amount of information on choices and directions to take. In terms of technology issues, membrane technologies appear to be targeted for future research. Nanomembranes and reverse osmosis were specifically identified, although ultrafiltration and microfiltration might be more appropriate to drinking water treatment applications. In these areas, research efforts should be tailored to the applications for current technologies.

Dr. Lucier commented on the progress related to LTG 1, including priority-setting and chemical selection. He added that he was pleased to see work on trenbolone. In 1998, Dr. Lucier evaluated trenbolone as part of a World Trade Organization panel focused on European questions concerning U.S. beef; at that time, there was little information on the risks involved in using trenbolone as a growth promoter. Dr. Lucier asked how trenbolone was selected as a priority chemical. Dr. Grey responded that interest in trenbolone arose from collaborations with Dr. Louis Guillette, Jr.; the initial studies were funded by the European Union. Dr. Grey and his colleagues were contacted by Dr. Guillette to measure androgenicity in CAFOs effluent in Nebraska. Dr. Gerald Ankley also was involved in attempts to detect trenbolone in the Nebraska CAFOs samples, but the compound is not stable, which complicated this research. Dr. Grey's laboratory was interested in the toxicology of the pure chemical and examined its effects in fish and rats.

Dr. Lucier asked about the apparent informality of the process for selecting chemicals for inclusion in the EDC program. Dr. Francis explained that the process varies. Directors use a combination of strategic planning and information from program offices or other outside entities expressing an interest in the program to identify potential compounds for future evaluation. The CAFOs issue arose as an area that the planning team identified several years ago when the program was asked to include in its MYP additional areas of interest if increased funds were available. The CAFOs issue was identified as a joint integrated project that would cut across the expertise found in many of the laboratories and centers and focus on a real-world situation. Funds have been cobbled together from existing resources, and CAFOs research has grown to

encompass effects, exposure, and risk management. A solicitation will be issued to engage the academic community (e.g., land grant universities), and partnerships will be developed through cooperative agreements. Plans to engage extramural partners currently are on hold because of EPA's budget situation, but the goal is to use the STAR program to build partnerships.

Dr. Lucier asked if EPA had considered evaluating package plants for water treatment in areas without a municipal wastewater treatment system. Is there any research to compare these plants with traditional wastewater treatment systems for efficacy of steroid hormone removal? Dr. Toth replied that basic processes in water treatment, such as sedimentation and flocculation, are being evaluated. The next phase will include research on a broader scale, and part of the plan is to evaluate the package plants. He also discussed chemical prioritization. The risk management program strives for a deliberative process for risk management evaluation, involving an assessment of the most relevant chemicals based on activity, recurrence, and exposure data. A list of resource questions associated with that analysis is generated, and an assessment of available skills and resources is made to determine which questions EPA can address.

Dr. Smith commented on the more formal or programmatic opportunities, such as region-sponsored workshops at which ORD scientists can be informed about regional needs. The regions are the end users of information generated by the scientists and also often raise issues that ORD should address. ORD tries to be responsive and often can adjust a program to respond to a specific region's needs; for example, extending CAFOs work to include dairy operations in California. Dr. Lucier described a project developed as part of an agreement between the Attorney General's office in North Carolina and Smithfield Farms to develop environmentally superior technologies to manage hog waste. Eighteen grants were awarded, and new technologies developed from these grants are now in use on model farms in North Carolina. The ability of these technologies to control odor, ammonia, and pathogen release was compared with emissions from hog lagoons, but steroid hormones in effluents were not evaluated because this work was not included in the original agreement. It may be useful for EPA to contact scientists in this program, which is coordinated by Dr. Michael Williams at North Carolina State University, to determine whether samples can be obtained to perform concomitant measurements of steroid hormone or other chemicals of interest and to assess whether the new technologies are more effective in reducing potential steroid hormone release.

Dr. Harding asked whether effluents from CAFOs and other types of discharges had been linked to human health outcomes and if EPA and the CAFOs program interfaced with epidemiologic studies to try to make the connection between contaminants in effluents and human health. Dr. Francis responded that this topic would be discussed in greater detail in the afternoon and that as of yet, none of the studies on effluents are taking place in the same geographic area as the epidemiologic studies on human health. Dr. Francis described a recent interview she gave for *The Washington Post*, which described 12 epidemiologic studies EPA is conducting in partnership with other agencies to broaden its research portfolio on human health effects. An intra-agency working group under the President's National Science and Technology Council has discussed a number of collaborative projects between agencies such as CDC, EPA, NIEHS, and NIOSH, among others. It was suggested that this group work jointly on the CAFOs issue and on wastewater treatment plants. Dr. Harding asked about interest in collaborative work with the American Water Works Association in terms of wastewater treatment research and whether this group might provide some funding. Dr. Toth commented on some limited collaborative work with this group, including cooperation on a filtration project assessing bank infiltration and emerging contaminants, including EDCs. USGS is performing some sample analysis, but this project is almost complete.

Dr. Francis commented that she has met with representatives from the Water Environment Research Fund (WERF) and has briefed its Executive Committee on several occasions. Members of WERF have met with Dr. Toth and his colleagues and have discussed a joint solicitation; however, because of EPA's funding situation, this collaboration has not moved forward. Drs. Francis and Toth have participated in panels to review projects arising from WERF grant efforts. In addition, Dr. Frederick Hauchman, who has been leading drinking water efforts, also works very closely with a global water research committee, and he has linked the two organizations because they are both very interested in EDCs.

Dr. Van Der Kraak commented that under LTG 1 intramural research and extramural research are being integrated. EPA is able to acquire needed expertise through extramural programs, including scientists working on basic science issues. This example of effective communication between researchers in academia and researchers at EPA could be disrupted if funding sources such as the STAR program are lost and researchers outside the Agency seek other funding opportunities. This serious concern should be made apparent to those controlling EPA's financial resources. Dr. Tillitt added that EPA relies heavily on outside researchers in wildlife toxicology. Without the STAR program, much of this capability could be lost.

Dr. James Lazorchak commented on EDC program collaborations with universities that are not necessarily driven by the STAR program. These studies are funded with other sources of money, and ORD collaborates with the universities by providing "in-kind" support (e.g., chemistry or gene expression expertise) that adds to the value of the study. These types of collaboration can be valuable, particularly for long-term studies performed by academics. A number of these studies currently are in progress, so despite the loss of STAR funds, these collaborations can continue to the benefit of all parties involved. Dr. Tillitt agreed that many opportunities for interagency collaborations provide advanced capabilities that EPA does not possess. He asked about a implementing a more formal mechanism for establishing collaborations of this sort. Dr. Francis commented that collaborations are useful and strongly supported if they are consistent with the direction set for the research program. Participants in these collaborations must ensure that other opportunities that may arise do not distract from the established research goals.

Dr. Safe commented that the research and presentations outlining efforts under this LTG highlighted sound and interesting science, but it was not clear how these efforts relate to human health. He explained that he has always been skeptical about the impact of EDCs on humans, mainly because the human diet contains many EDCs and compounds that modulate endocrine pathways. He would have liked to have seen more effort explaining how researchers can or cannot extrapolate some of the laboratory animal models and wildlife models to humans and what animal models are best for extrapolating effects to humans. He expressed a desire to see more of a connection between the laboratory animal and wildlife models, which are very well done, and use of these models to make predictions on the impact of environmental EDCs on human health.

A participant noted that some animal models are used for specific types of research that are optimal for predicting impacts in humans. For example, birds have hollow bones and are a good model for osteoporosis; in addition, the metabolism and use of vitamin D and its metabolites are very similar in birds and humans. Similarly, if one looks at fundamental neural processes, the expression of behavioral responses or the hypothalamic-pituitary-gonadal axis responses may vary somewhat between classes, but the fundamental biology and mechanisms are likely to be similar. The problem with EDCs is that the adverse effects need to be assessed in different classes, and then perhaps connections can be made to humans. Some experimental animals also

might have certain properties, such as neural plasticity, that are lost in humans, so it is possible to ask questions that cannot be pursued in humans concerning what might be recoverable or whether new cells are made in these species' brains.

Dr. Francis commented that this question touches on the ultimate research goals of the program, which include the ability to define the impact of EDCs on humans. It is hoped that the projects described at this meeting and the path set out by the program will help attain this goal. As an example, Dr. Vickie Wilson's group is working to build a foundation for making cross-species correlations. Some of the epidemiologic studies the program has funded will assist this effort. Dr. Shaina Swan is using tools developed by Dr. Gray and colleagues to examine the impact of exposure to androgenic compounds on development. These tools are used in Dr. Swan's epidemiologic studies to determine whether there is an association between human exposures and certain endpoints. Dr. Michelle Marcus previously conveyed to Dr. Francis the benefit of attending workshops that bring together toxicologists and epidemiologists, which allows for sharing the various tools that each of these disciplines have developed and application to their respective studies.

Achieving the goal of determining the impact of EDCs on human health will require work by intramural scientists, extramural scientists, and members of other federal agencies. Dr. Safe commented that one approach to linking EDCs to human health effects may be to take information from human epidemiologic studies and use animal models to determine the mechanisms causing the effects observed in these studies. A participant commented on his work identifying membrane progesterone receptors in fish and human membrane receptors found on sperm. Collaboration with epidemiologists at an EDC meeting held in Japan revealed a decrease in the receptor protein in subfertile males (fertility clinic patients), and a toxicology study now is in progress. Lower vertebrates, particularly fish, can be useful models for analyzing effects that are difficult to observe in mammalian models, emphasizing the importance of crosstalk between researchers focusing on humans and other mammalian species and those focusing on lower vertebrates or invertebrates. Dr. Gray commented on interspecies extrapolation; in many studies, researchers are trying to work with target tissue exposure levels for the adverse effects. Other analyses include serum models and amniotic fluid levels of some of the suspected EDCs; researchers then attempt to link this information to human exposure levels.

Dr. Lucier commented that the posters describing dosimetry studies with cross-species comparisons contained excellent information that should be useful in reducing uncertainty and helping to inform risk assessment. He also complimented some studies on cumulative exposure that analyzed common mechanisms as well as differential mechanisms and common endpoints reached through different mechanisms. The studies on cumulative risk also were very good; cumulative risk assessment data can be weak, but research in progress will help strengthen them. The dose-response issues also were addressed appropriately, although more about the consequences of physiological levels of exogenous hormones is needed. This perhaps could be included in research on biologically based models for endocrine disruptors and eventually included as part of the Computational Toxicology Program. Dr. Francis commented that a recent RFA issued by the Computational Toxicology Program solicited research based on a systems biology approach. Research completed through the Computational Toxicology Program will make it easier to follow linkages from effects at the molecular level up to the organism level and will aid in extrapolation of effects between species.

Working Lunch

Dr. Harding opened the discussion with questions about an EPA-funded initiative issued in 2002, which was directed at CAFOs research. This initiative was not specifically supported, although EPA did manage to proceed with some of the research. Subcommittee members agreed that the initiative should have been funded, because CAFOs are potentially a large problem in most states, and EPA is the most suitable agency for performing research on this issue. Dr. Safe commented that the EDC program should set research priorities based on major global contamination, regional problems, and any site at which potentially harmful chemicals are released. CAFOs appear to fit these guidelines.

Dr. Tillitt thought there was enough material to report on LTG 1. Most of the challenges and questions were addressed; presentations during the afternoon of Day 2 provided additional information. Dr. Lucier commented that the LTG 2 posters were probably the weakest, although the goals still were met. Many of the LTG 1 posters were relevant to questions posed under LTG 2, such as EDC effects on wildlife. He thought that the distinction between LTG 1 and LTG 2 was in some ways artificial because the effects of EDCs on wildlife cannot be determined without examining cross-species, dose-response, and exposure issues, which are addressed in other LTGs.

Dr. Safe commented on the inadequacy of the extrapolation of results obtained in animal model systems to humans. He would have liked more research showing how wildlife problems relate to human health or how laboratory animal models can be extrapolated to humans. Rats might not be a good model system for humans, especially for low-dose effects of endocrine disruptors. Rat chow has phytoestrogens; the human diet contains even larger amounts of phytoestrogens, which are present in foods such as fruits, nuts, and vegetables, and these may influence low-dose effects. Dr. Lucier agreed that endogenous levels of estrogens can lead to either increasing or decreasing sensitivity to EDCs, depending on the dose. Although understanding the effects of endogenous estrogens would be worthwhile research for EPA to perform, it would require collaboration with FDA. Current levels of interaction between the EDC program and FDA appear to be inadequate.

Referring to the link between environmental EDCs and human health, Dr. Harding asked whether EPA has any input on deciding what biomarkers to target in human exposure studies performed by other agencies such as CDC. Dr. Francis commented that members of the EDC program have positions on the committee that makes recommendations concerning the chemicals examined in these studies; for example, the EDC program recommended assessing phthalates.

Dr. Safe noted that humans may ingest large enough amounts of estrogens that estrogens from other sources may not have an effect. Ingested estrogens also may reduce the dose of anti-androgens needed to overcome the threshold for a response. A literature search yielded a paper questioning health concerns about industrial compounds or byproducts in parts per trillion concentrations when micromolar levels of endocrine-active compounds are found in food. Dr. Lucier pointed out that the effects of background levels of estrogen, either from dietary or endogenous sources, must be considered to understand dose response. Dr. Safe added that to pursue this research, EPA should arrange a joint effort with FDA. Dr. Tillitt suggested that even if endogenous concentrations of estrogens are known, it still is necessary to understand mechanisms of action and binding efficiencies. Dr. Safe commented that fewer resources might be allocated to questions concerning human health issues if environmental concentrations were shown not to have an effect because of high background levels of estrogens. Nevertheless,

potential EDCs in the environment should not be ignored, and research on understanding mechanisms of action should proceed. Dr. Lucier added that if endogenous levels already exceed the threshold for a response, in some cases the dose response level is already saturated. Relative amounts may indicate that additional exposure creates a small risk; it would be difficult to argue that additional exposure poses no risk.

Dr. Van Der Kraak asked how work funded by EPA relates to work funded by NIH and whether any research funded through NIH addresses environmental chemicals. Dr. Francis responded that a joint RFA with NIH was issued to investigate population-level effects in wildlife and humans. The wildlife research proposals were strong, but the proposals addressing human health were not as promising. Of the 12 grants funded, 9 focused on wildlife effects. The proposed human health studies did not address what EPA considered to be population-level effects, so a new joint RFA was issued. Dr. Harding asked whether studies such as the Children's Health Initiative are assessing the effects of EDCs. Dr. Francis answered that the National Children's Study addresses endpoints related to growth, onset of puberty, and obesity.

Dr. Lucier asked about EPA efforts to address research to examine inter-individual variation and genetic susceptibility, and how this research might relate to the EDC issue. He commented that this information would be important for risk assessment, addressing uncertainty factors, genetic variation, and sensitive subpopulations. Dr. Francis explained that EPA has some biomarker studies, but they are conducted under a different program. Dr. Lucier asked to see a 1- to 2-page summary of ongoing activities relevant to the EDC program. Dr. Francis added that EPA still is assessing how much research on biomarkers the Agency should sponsor. A separate biomarkers program to support work on genetic polymorphisms has been initiated. Dr. Lucier commented that work of this sort probably was underway at NIH as well, particularly at the National Human Genome Research Institute (NHGRI). EPA could mine information from NIH and use it for risk assessment and developing guidelines for both cancer and noncancer effects.

Dr. Harding asked about the decision made in Sweden to remove phthalates from children's toys, and whether this decision was based on available research. Commenting on California's decision-making process, a participant described how protection of the resource (the precautionary principle) is the initial impetus for such a decision. The regulatory approach in California consists of implementing rules set by federal agencies. Dr. Francis quoted an individual from the Consumer Product Safety Commission (CPSC) who stated that CPSC is waiting for EPA to make a regulatory decision about phthalates because EPA is the agency responsible for designating a chemical as an endocrine disruptor and setting allowable levels.

Dr. Tillitt asked the Subcommittee to discuss EPA progress in determining low-dose effects. Substantial progress has been made in trying to understand these effects, the U-shaped dose-response curves, and the combination of mechanisms that might cause them. Dr. Safe commented that less progress has been made in understanding mechanisms. Dr. Lucier noted that work on thyroid hormone action addressed dose response and effects on the hypothalamic-pituitary-gonadal axis; several posters addressed mechanisms and low-dose effects. Dr. Francis commented that a solicitation for research addressing low-dose effects was issued earlier in 2004. Work by these grantees was not included in this meeting because it is in the very early stages. Two of these grants focus on the thyroid system, and a third on cadmium. Dr. Lucier said that he did not see much modeling, in terms of dose response, aside from a poster by Hugh Barton. He mentioned several good studies on dose response for wildlife and several studies on environmentally relevant levels. Dr. Tillitt added that some very ambitious, but necessary, research is examining latent effects. Dr. Francis commented that the EDC program sponsors

human toxicology work that includes endocrine disruptors; she agreed to provide a summary of this work to the Subcommittee.

Dr. Lucier asked how the EDC program determines when dioxin is included as an endocrine disruptor. Dr. Francis responded that ORD made the decision to exclude dioxin from the EDC program, and include it in the Human Health Program. Dr. Lucier noted that dioxin sometimes falls under the EDC category. Dr. Francis replied that dioxin research has been excluded to conserve program resources. The program has funded extramural dioxin research grants, and intramural research projects that examine multiple chemicals, including dioxin. Dr. Harding noted that members of the program participate in work groups and advisory boards that examine dioxin-related issues.

LTG 2: Determining the Impact of EDCs on Humans, Wildlife, and the Environment

Dr. Gregory Toth
National Health and Environmental Effects Research Laboratory

Research pertaining to LTG 2 involves determining the extent of the impact of endocrine disruptors on humans, wildlife, and the environment using methods, models, and measures developed by ORD and others outside EPA. LTG 2 research questions ask:

- ✧ How and to what degree are human and wildlife populations exposed to EDCs?
- ✧ What effects occur in exposed human and wildlife populations?
- ✧ What are the chemical classes of interest and their potencies?
- ✧ What are the major sources and environmental fates of EDCs?

Results of exposure and effects research performed under LTG 2 will be integrated across the risk management paradigm and used by states and regions. ORD has a unique complement of molecular biology and bioinformatics core capabilities that can be applied to these efforts. Research areas covered by posters presented for this LTG include impacts on aquatic wildlife and on humans.

Assessing the impact of EDCs on aquatic wildlife includes application of molecular indicators to a range of sources including CAFOs, wastewater treatment plants, and pulp and paper mills, with a focus on EPA's aquatic toxicity model (fathead minnow assay) and concomitant research in chemistry and biology. Past accomplishments in these areas include identification of androgenic activity in effluents from CAFOs and pulp mills, estrogenic activity in effluents from wastewater treatment plants, and whole lake ecosystem studies of synthetic estrogen effects. These efforts help support EPA's Office of Water in considering potential risks from CAFOs and wastewater treatment plants and have helped establish partnerships among ORD and state and regional environmental scientists, engineers, molecular biologists, and managers. Future research efforts include integrated CAFOs research including exposure, effects, and risk management issues; development of a range of specific molecular diagnostic indicators for the fathead minnow; chemical research paired with sample fractionation; and endemic species/chronic exposure issues.

Research under LTG 2 also will attempt to characterize the impact of EDCs on a larger scale and population basis. Previous work in this area includes examining the effects of EDC exposure throughout the entire reproductive and early development stages in fish and how these might affect population dynamics, and application of molecular diagnostic indicator methods to endemic fish on a regional scale in partnership with EPA's Environmental Monitoring and

Assessment Program (EMAP) studies of the Ohio River Basin. Research also is ongoing to understand the effects of EDCs on invertebrates, with work on these species aimed at developing strategies for monitoring EDC flux between the water column and sediment to significantly expand the understanding of endocrine signaling pathways in invertebrates and determine whether invertebrate genes can be used as indicators for EDC monitoring.

ORD also monitors EDC exposures as part of major children's health studies. Data from these studies inform EPA efforts to examine exposure to other classes of chemicals and for other age ranges. Posters in this group examine the potential effects of EDCs on changes in puberty timing, whether EDCs may underlie decreased sensitivity to progesterone in endometriosis, and whether exposure to brominated flame retardants is associated with a number of endocrine-sensitive endpoints in women or their daughters. A multi-agency RFA, issued in 2000 by EPA, NIEHS, NIOSH, and NCI supports research examining the relationship between EDC exposure and various reproductive or developmental effects in humans, including fertility, pregnancy outcomes, and hormonally mediated reproductive tract cancers in offspring exposed *in utero*.

Overall, research under LTG 2 provides unique data on the extent of EDC impact on humans and aquatic wildlife. ORD has built the framework to provide regional-scale, multiple compartment aquatic ecosystem EDC characterization. Data are provided in the context of problem-driven risk assessment and management, and ORD provides leadership to the global EDC exposure research community.

LTG 2 Discussion Session

Dr. Harding called for comments and questions from Subcommittee members. Dr. Lucier opened the discussion on the two main categories of research presented during this poster session: wildlife studies and human health studies (which included epidemiologic studies conducted under joint arrangements with technology transfer activities). He was unsure how LTG 2 was established, given that the posters were not always consistent with the scientific questions posed under this goal. He said that overlap between LTG 1 and LTG 2 is understandable. Assessing the effects of EDC exposure on wildlife requires examining issues relevant to risk assessment, dose response, sensitive subpopulations, and cumulative risk assessment, all of which are part of the risk assessment process for groups of chemicals, including EDCs. Dr. Lucier commented that the material presented in this session was well done, particularly wildlife studies, "poisoned lake" studies, and studies of ethinyl estradiol equivalents in CAFOs. EPA appears to collaborate with agencies such as NIOSH, NIEHS, and NCI on epidemiologic studies. The Agency should take more credit for these multiagency initiatives because EPA played a major role in developing the collaborations. Several studies examined genetic predisposition markers, such as markers for metabolizing enzymes. Dr. Lucier suggested that the next round of epidemiologic studies incorporate these markers; in addition, samples could be stored and assessed for new markers as they become available. The studies encompassed a good mix of assessing effects on growth and development, cancer, and reproduction. A mechanistic study on the effect of aberrations in progesterone pathways on endometriosis might have been better placed in LTG 1. Overall, Dr. Lucier was favorably impressed with the work presented during the LTG 2 poster session.

Dr. Van Der Kraak, who also was charged with reviewing LTG 2, commented that the research was well presented and clearly represented state-of-the-science work, particularly for the wildlife studies. EPA has done a good job of integrating researchers from different laboratories and bringing appropriate expertise to bear on different questions, especially for CAFOs. He also

complimented EPA's interactions with outside partners, such as on a project examining contamination of a Canadian lake. The Canadian system was unable to fully fund this project, so Dr. Van Der Kraak was encouraged to see that other sectors have provided funding for EDC research. He commented positively on invertebrate research, adding that these projects used strong tools to address the effects of EDCs in invertebrates. The human health studies also were effective, and although lacking in definitive answers, ongoing research would address important questions in this field.

Dr. Harding commented that the epidemiologic studies were very comprehensive and aggressive in terms of research approaches. She had questions concerning EPA's niche in human health studies; to her understanding, EPA is charged with defining the connection between human health and the environment. She asked for clarification of EPA's niche relative to that of NIEHS on some of the biomarker studies, and how EPA's role differs from that of NIEHS or CDC. She also asked whether large, expensive epidemiologic studies are sustainable in the long term. How are these studies funded? Dr. Roy Fortmann responded that these types of studies, which are designed to collect basic information to understand the routes and pathways of exposure and factors that affect exposure, are very focused and unlikely to be repeated. One of the goals of a study performed in collaboration with CDC is to determine the relationship between spot urine samples collected in the study and environmental measurements and routes and pathways of exposure to pyrethroid metabolites, for example. The results of these sorts of studies will provide information that will be used to design future smaller, more focused studies.

Dr. Fred Hauchman addressed the questions about EPA's research niche. EPA's niche is to examine the entire risk management and risk assessment paradigm, something that neither CDC nor NIH does. CDC collects biomarker data but not data on exposure. NIEHS examines the toxicity of a chemical but not the source or how to reduce exposure or develop mitigation strategies. EPA examines the entire range of issues, including source of exposure, levels that result in health effects, and ways to reduce exposure. Dr. Harding countered that some NIEHS pesticide studies collect biomarker data and information on exposure pathways. Dr. Hauchman responded that EPA studies the fundamental science of effects, activities, and causes of exposure so that risk mitigation strategies can be developed. An epidemiologic study could determine that a pesticide caused an event but may not collect data concerning when, how often, the magnitude of exposure, and how exposure relates to a dose-response curve. Dr. Francis added that similarities exist between some of EPA's programs and programs at NIEHS, but EPA research is more targeted to the needs of the Agency, whereas NIEHS research programs address issues at a much broader level and may not necessarily target the questions that would help EPA support or develop a regulation, or a tolerance program, for example.

Dr. Safe commented on his pessimism regarding organochlorine studies. Generally, if an effect does not correlate with one PCB, researchers move on to another and can continue to do this indefinitely. He conceded that the examples presented in this poster session were good because they were not just background level studies; instead, these studies focused on special exposure groups and are more likely to identify real effects. The studies could be strengthened by including more of the older classes of endocrine disruptors, including organochlorines. Dr. Safe commented on the usefulness of examining phthalates and pregnant women; phthalates can be measured and divided into groups to correlate exposure with an effect. A participant responded that when the RFA was written, preference was given to studies concerning new EDCs, rather than traditional organochlorines. There also was difficulty at the time in identifying an exposed population large enough for a strong epidemiologic study. Dr. Francis added that EPA strongly advised NIEHS to include chemicals other than PCBs and dioxin, but NIEHS disagreed.

Ultimately, EPA chose to fund some of the more nontraditional EDCs, such as the phthalates, heptachlor, and polybrominated diphenyl ethers (PDBEs). Thirteen projects were chosen for external peer review, resulting in the funding of two of the studies, which examined persistent organic pollutants (POPs) and chemicals such as dioxin. Dr. Safe commented that he agreed with including POPs because the outcomes the studies examined were possibly endocrine related.

Dr. Tillitt was impressed by the attempts and progress made in identifying some of the classes of compounds discharged into the environment, including those that will affect fish and wildlife health. He approved the idea of using the Toxicity Identification Evaluation (TIE) approach on CAFOs, pulp mills, and air monitoring and asked about plans to use this approach with wastewater treatment plants. Dr. Lazorchak noted that recent discussions focused on attempts to identify estrogenic or androgenic activity and the compounds causing this activity. The solution is to use a fractionation or TIE approach, but the study has not yet been designed. He added that a study on effluents to identify estrogenic nonylphenols used chromatograph separation techniques. Dr. Marc Mills added that this approach was not as formally structured as TIE but was initiated with the nonylphenols to try to separate complex mixes. Dr. Lazorchak commented that the TIE process will determine categories of exposure, such as what portion of the waste is androgenic or estrogenic or both, but does not determine effect.

Afternoon Work Session

The Subcommittee members used the Tuesday afternoon work session to organize Wednesday's oral report. Dr. Harding asked that all sections be submitted to her. Dr. Lucier offered to draft the section on LTG 2 as an outline for Wednesday's presentation and then send a formal written version to Subcommittee members before the January 6 conference call to allow other members to comment on it. Dr. Harding asked each working group to organize their writing to respond to the charge questions in a systematic way; in the morning, the material will be collected and printed so that all members can review it. The Subcommittee members agreed that Wednesday's presentations would not include visuals. The spokespersons for each section of the report were as follows:

- Dr. Don Tillitt, LTG1
- Dr. George Lucier, LTG2
- Dr. Glen Van Der Kraak, LTG3
- Dr. Juarine Stewart, Resources
- Dr. Anna Harding, Leadership

Dr. Avery advised the Subcommittee members that whatever is presented in the oral report on Wednesday becomes public information; therefore, the members may want to limit the detail. More details can be included in the report to the BOSC Executive Committee. Dr. Avery also advised the Subcommittee members that if all members meet for a work session before the presentation, that session must be open to the public. The Subcommittee members decided to work first in subgroups to organize their writing and then provide bullet points to Dr. Harding. The oral report will be rather superficial, with expectations that more information will be added to the final written report. Dr. Tillitt thought that most of the statements in the report will be positive; the Subcommittee members agreed but decided they needed to come to agreement on any challenges to the program that would be presented in the oral report. Members also discussed whether recommendations would be discussed in the oral report. Dr. Avery advised that the general impressions of the meeting and summaries of the discussions would be part of

the public record and cautioned members on providing recommendations at this point. The Subcommittee's recommendations should go to the BOSC Executive Committee, not directly to EPA.

The Subcommittee members discussed whether they should include recommendations in the report. Dr. Safe asked if the oral report should include only general, nonspecific statements that will not compromise the final report. Drs. Harding and Boyd thought that the report should identify challenges and avoid specific recommendations. Dr. Avery reiterated that recommendations cannot be made directly to EPA and reminded Subcommittee members that anything presented in the oral report on Wednesday would be part of the minutes and part of the public record even if the oral report itself was not written down. Dr. Harding decided the best approach would be to discuss strengths and challenges and not to provide recommendations. The recommendations will be drawn out of the challenges and will be provided in the final written report. She asked each subgroup to focus on the charge questions for each of the LTGs and report on issues they could discuss comfortably.

Dr. Van Der Kraak was uncomfortable preparing a separate oral report for each LTG because many of the comments will be similar across all LTGs. Dr. Lucier agreed that some of the challenges are common particularly to LTG 1 and LTG 2, such as identification of sources, applying new technologies to study health effects, epidemiologic studies, human studies, wildlife studies, and ultimately integration of these diverse studies. Working with other agencies that have overlapping goals also is a challenge common to both of these LTGs. LTG 3 clearly is responsive to EDSTAC legislation, but those duties are nearly complete. Dr. Safe recommended as an alternative that the groups contribute to a common presentation they could be developed between 10 a.m. and 12:00 noon on Wednesday, rather than have three nearly similar presentations.

Dr. Van Der Kraak stated that his group found that ORD has made good progress on LTG 3 and that the work is completed or close to completion. He expressed concern that a message that the work is completed could result in reduced funding for the program. Dr. Lucier agreed but thought that ORD would continue to assist OPPTS in validation and pre-validation duties. Dr. Francis commented that ORD not only serves as a consultant in this process but also assists in the prioritization and use of new technologies, including methods allowing better use of fewer animals. The duties of ORD go beyond the EDSTAC legislation; the tools provided to OPPTS by ORD will continue to evolve.

Dr. Harding discussed specific issues the report needs to address, such as whether ORD is sufficiently flexible to adapt to and anticipate future research needs. She thought the best approach was for each working group to prepare a summary for the oral report. She then would consolidate and present the report, avoiding repetition of the same strengths and challenges described for each LTG. The Subcommittee members broke into working groups to develop their sections of the report.

Wednesday, December 15, 2004

Relevance of the Endocrine Disruptor Research Program – OPPTS Perspective
Mr. Joseph Merenda
Director, Office of Science Coordination and Policy

Mr. Merenda described how research performed by the Endocrine Disruptor Research Program is used to support EPA regulatory activities. Overall, the interaction between the research program and regulatory activities has proven to be a very effective partnership. The research program preceded regulatory efforts, which were initiated when endocrine mechanisms were recognized as contributing to the carcinogenic, reproductive, and developmental toxicity of some chemicals. In 1996, the FQPA and SDWA mandated that EPA develop a screening and testing program to identify substances with estrogenic effects in humans. This mandate subsequently was expanded to include endocrine effects other than estrogenic effects. EPA formed EDSTAC to provide advice on how to design a screening and testing program for endocrine disrupting chemicals. Key EDSTAC recommendations included a focus on chemicals affecting estrogen, androgen, and thyroid hormone systems, examination of the effects of these chemicals on humans, wildlife, and the environment, development of a priority setting process for examining a broad range of chemicals, and development of Tier 1 screens (identify a substance's potential for endocrine interaction) and Tier 2 tests (to generate data for risk assessment).

Factors limiting implementation of EDSTAC recommendations included a paucity of data on endocrine effects for priority setting, inadequate QSAR tools as a surrogate, an unsuccessful trial using a high throughput pre-screening approach, and a lack of optimized and validated Tier 1 and Tier 2 assays. EPA subsequently decided to use exposure data to choose 50 to 100 chemicals for initial screening. Optimization and validation of assays has presented significant scientific challenges, and ORD collaboration with OPPTS has been crucial to overcoming these challenges. Collaborations with the OECD also are underway to ensure international acceptance of EPA guidelines and validated assays.

ORD has played an important role in development, optimization, and validation of Tier 1 and Tier 2 assays, developing initial protocols for many of these assays, such as estrogen and androgen receptor binding assays, steroidogenesis and aromatase assays, and a fish reproduction screen. ORD has advised OPPTS on protocols for the Hershberger assay and amphibian growth and reproduction tests, and conducted optimization studies for pubertal and frog thyroid assays. Although many of the protocols for these assays are well established, validation standards for assays used in a regulatory capacity are much higher than those for research assays. Besides providing guidance for validation of the assays, ORD also recommends reference chemicals and dose levels, and assists OPPTS in identifying causes of variability seen in contractor validation data for some assays. ORD also is involved in development of second generation assays and tools, focusing on reducing use of animals and allowing higher throughput.

ORD is involved in application of endocrine assay results for risk assessment. ORD has issued RFAs to assess low-dose effects of EDCs, and ORD research on endocrine-mediated reproductive and developmental effects aided OPPTS decisions on vinclozolin, atrazine, and cumulative risk for chlorotriazines. ORD research aimed at understanding susceptible life stages also directly affected OPPTS risk mitigation decisions. Once large-scale EDC screens are established, other programs within EPA, outside of OPPTS, will be involved in EDC screening and ORD will continue to support these ongoing activities.

Relevance of EDC Research Program: Regional Perspective

Dr. Barbara (Bobbye) M. Smith
Region 9

ORD contributes to the decision-making processes of the regions by obtaining information concerning regional research needs; providing expertise, resources, and advice to support the research; and interacting with regional scientists and managers. Recently, several workshops have been held to convey region research, regulatory needs, and interests to ORD, including the ORD/Regions Emerging Pollutants Workshop, held in August 2003, and the Animal Feeding Operations Workshop, held in December 2004. These workshops brought to ORD's attention the need for tools to assess known and potential EDCs present from sources such as wastewater treatment plants, Superfund sites, and effluent from CAFOs.

ORD provides technical advice, technical support, technology transfer, and technology implementation assistance to the regions. Regional science needs include exposure tools for both "model" and "new" EDCs and emerging pollutants, research to determine connections between new tools (including molecular biology and genomics information) and human health outcomes, research concerning modes of action (for risk assessment), and pathway assessments to determine fate and transport of EDCs and emerging pollutants.

ORD provides technical support to the regions in response to their specific needs. For example, ORD assisted scientists in Region 8 on implementation and analysis of the plasma vitellogenin assay to detect suspected EDC activity in Boulder Creek, downstream of a wastewater treatment plant. When scientists in Region 3 found intersex bass in the South Branch Potomac River, ORD collaborated with the region to analyze potential sources of EDCs and perform laboratory exposures to assess the presence of estrogenic EDCs using the vitellogenin gene expression assay. ORD also is providing technical support to Region 5 to develop chemical analytical methods to detect alkyl and nonyl phenols. Finally, ORD is collaborating with Region 9 to modify the ORD-developed fathead minnow vitellogenin gene expression assay for use in rainbow trout to allow California to monitor cold water habitats (the fathead minnow assay is used to monitor warm water habitats).

Other interactions between ORD and the regions include providing technical advice and support to for site-specific or problem-driven research, technology transfer to regions through ORD initiatives, and $2 million in extramural funding. ORD also provides liaisons to Regional Science Programs and supports the Regional Research Partnership Program (R2P2), which sends regional scientists to ORD laboratories to learn new technologies and transfer this knowledge to their respective regions. Regions also train their staff regarding ORD protocols and new molecular fields of research to enable effective technology implementation. Regional Science Liaisons also serve as direct links between ORD and the regions and states to inform ORD of regional scientific needs.

Agency Comments

Dr. Elaine Francis
National Center for Environmental Research

Dr. Francis provided closing comments, focusing on a bibliometric analysis of the publications resulting from the EDC program to help the Subcommittee members assess the program's scientific relevance and impact. Ninety-six of the 390 articles resulting from the program were

omitted from the analysis. The analysis was performed using Thomson's Institute for Scientific Information *Essential Scientific Indicator* (ESI) and the *Journal Citation Report* (JCR).

The program's papers covered 11 of the 24 ESI fields, such as pharmacology, toxicology, clinical medicine, and chemistry. This indicates that the program sponsors a diverse array of research that cuts across a variety of fields. Average cites per paper ranged from 1.5 to 51. The program had papers in the top 1 percent of four fields (i.e., environment/ecology, pharmacology/toxicology, multidisciplinary [refers to work found in journals such as *Science* and *Nature*], and plant and animal science). Four papers in the environment/ecology field had an average citation rate of 90.75 per paper.

The ratio of average cites to expected cites (good is greater than 1) also was analyzed. Cites for EDC program publications ranged from 0.9 to 4.69 across 11 fields. The JCR Impact Factor (a measure of the frequency with which the average article in a journal has been cited in a given year) showed that 129 EDC program publications (44%) appeared in the top 10 percent of journals. The JCR Immediacy Index (a measure of how quickly an average article in a journal is cited) indicated that 60 of the papers appeared in the top 10 percent of journals. The self-site rate was low, approximately 3 percent (less than 10% is desirable). Overall, this analysis found that "EPA-EDC papers generally exceed the expected citation rates for the journals and years reviewed."

Dr. Francis concluded her presentation by promising to provide to the Subcommittee members additional budget information and IRIS assessments by early January. She thanked the Subcommittee, principal investigators, and others who assisted with and participated in this review.

Questions for Dr. Francis

Dr. Tillitt asked about the connection between information going into and coming out of EPA's Risk Assessment Forum. Dr. Francis responded that the Risk Assessment Forum is a body of scientists from across the Agency that take on crosscutting risk assessment issues, developing white papers and documents that serve as guidance. The Risk Assessment Forum is coordinated by the National Center for Environmental Assessment (NCEA). There is limited interaction between the Forum and the EDC program. The Science Policy Council is another group that examines crosscutting science policy decisions across the Agency, promoting discussion of these issues.

Work Session

Dr. Harding asked the working groups to report on their assigned LTGs. Dr. Lucier responded that the LTG 2 report begins with general comments summarizing the goal and then addresses the charge questions; it does not comment on leadership, resources, or budget issues. Dr. Van Der Kraak stated that the draft report he wrote with Dr. Tillitt discusses the LTG in terms of program design, relevance, progress, strengths, and challenges. Dr. Stewart evaluated budget issues but needs additional budget information. She noted that Dr. Harding may wish to omit some of the recommendations in her section of the report for the oral presentation.

The Subcommittee decided that Dr. Harding should mention the materials received and reviewed by the Subcommittee and then address each LTG separately, presenting findings on program design, relevance, and progress as they pertain to each goal. Dr. Safe commented that the

Subcommittee had not addressed the definition of "endocrine-disrupting chemicals." Currently, a substance is considered an endocrine disruptor if it elicits an endocrine-related response, but there is no clear-cut basis for inclusion or exclusion in this category, as demonstrated by the indeterminate status of organochlorines, PCBs, and dioxin. Dr. Lucier added that phthalates constitute another category of chemicals that are sometimes, but not always, classified as EDCs.

Dr. Harding asked how the Agency decided to classify a given chemical as an EDC. Dr. Lucier responded that, historically, the legislation referred to estrogen-like substances. EPA broadened this definition to include androgen, androgenic activity, and thyroid hormone, but decided at the time not to include dioxin, although PCBs was included. Other organochlorines, but not dioxin, also were included because the Agency did not know how dioxin fit into the context of its research framework, both in the EDC program and elsewhere in the Agency. Dr. Safe commented that perhaps the definition for EDCs should encompass anything that provokes an endocrine-related response. Dr. Lucier agreed that the definition of EDC seemed to be a moving target and that perhaps EPA should take the lead in establishing a definition that fits its program as well as some of the other activities in this country and around the world.

Dr. Harding asked whether this subject should be included in the oral report or saved for the written report. Dr. Safe thought it should be included as a small criticism. Dr. Van Der Kraak mentioned another criticism; from the human health perspective, EPA did not have many examples that linked EDCs to human health issues. This link was made only on posters concerning the potential effects of dioxins on endometriosis and puberty. A new definition should explicitly include the whole range of chemicals with endocrine-related function, including dioxin. Endocrine disruptors initially were identified in *in vitro* assays, which focused on phenol-like compounds; other compounds were excluded. At this time, it may be more appropriate to focus on function rather than the identity of the chemical. Dr. Lucier added that NIEHS originally called these compounds environmental estrogens, then defined them as hormonally active xenobiotics. The endocrine disruptor definition was derived from EDSTAC proceedings.

Drs. Safe and Lucier agreed that the definition of endocrine disruptor has been broadened to include anything that elicits an endocrine-related response, and it is not always clear which substances are included and which are not. Dr. Lucier reiterated that EPA should develop a broad-based definition that the entire community can use; the definition should cover all substances that modify endocrine activity or elicit an endocrine-related response. The definition should be agreed on and used by many agencies, not just EPA. Drs. Safe and Harding recommended that this issue be included in the introduction of the oral report.

Dr. Harding asked if any of the working group reports discussed the Computational Toxicology Program. Dr. Van Der Kraak mentioned the program when acknowledging EPA's accomplishments in this field and the use of computational toxicology in prioritizing research on compounds and sources.

Dr. Harding asked members if they agree that scientists in this program are at the forefront of EDC research and their work serves as a benchmark for ongoing research. Dr. Lucier thought EPA's efforts were strongest in the areas of ecological and wildlife health. Dr. Van Der Kraak concurred and stated that EDC program scientists are at the forefront of the development of testing methodologies and show emerging expertise in using some of the best analytical approaches to CAFOs, sewage treatment, and pulp mills. Dr. Lucier added that EPA scientists also are experts in source identification as it relates to exposure; EPA has more expertise in this

area than CDC, and no other agencies perform this type of work. The EDC program also is a leader in development of mammalian tests, not just ecological tests; EDC Program scientists, however, are not at the forefront for mechanisms of endocrine action or for "omics" technology. Dr. Lucier noted that EPA should not be expected to be a leader in the "omics" fields because other agencies are charged with this work, but EPA has been successful in leveraging that information to address its mission. Dr. Safe commented that EPA could do more in this field. Dr. Tillitt agreed that EPA could put more effort into using "omics" technology for human health study, but the Agency currently is at the forefront for wildlife testing using this technology (e.g., the fathead minnow assay).

Dr. Harding acknowledged that EPA does benchmark research on the ecological side, but she asked if the Agency is at the forefront of research on human health. Dr. Lucier and Dr. Safe thought that EPA could strengthen its efforts in human health research; NIEHS is stronger in this area. Dr. Tillitt commented that, within its niche, EPA is at the forefront. NIEHS and universities are generating a great deal of information, but EPA takes that information and applies it to its mission, facilitating development of an applied model that eventually will be used for risk assessment.

Dr. Boyd stated that in the area of risk management, EPA's biggest strength is in CAFOs, but the Agency must strengthen its efforts in sewage and wastewater treatment to equal efforts outside EPA, both nationally and internationally. Although the Agency is capable of being a leader in these areas, it is not perceived as such. Dr. Harding decided that the oral draft report would highlight areas in which EPA serves as a benchmark; the areas of weakness would be discussed in the written report.

Dr. Lucier returned to the issue of EPA's work in the "omics" fields. EPA has correctly decided not to play a leadership role in these areas but instead to apply information generated by others to its own efforts. The challenge EPA faces is to find mechanisms for doing this efficiently, with respect to time, money, and resources. For example, EPA does not need a Center for Toxicogenomics, because NIEHS has one. Dr. Van Der Kraak commented that although EPA may not be a leader in the field of, for example, zebrafish genomics, it is a leader in the development of the fathead minnow assay, which uses new technologies. Difficulties in evaluating EPA efforts in "omics" technologies arise when a distinction is made between intramural and extramural research. If EPA funds a grant to a researcher who is an expert in a given field, does that imply that EPA has that expertise? Drs. Stewart, Safe, and Harding agreed that EPA should get credit for the expertise it funds. They added that it might be appropriate to comment on the STAR program with respect to extramural expertise because this program fills a number of intramural research gaps.

Dr. Van Der Kraak thought EPA's methodology and approaches are near the benchmark for research at the interface between testing and screening for environmental chemicals. EPA is not a leader in wastewater research, although its efforts are advancing. The Agency also has responded quickly to issues arising from CAFOs and is a leader in this area. Dr. Boyd agreed that with its accomplishments in CAFOs, EPA could move ahead of other organizations that do not have its history or background in treatment issues.

Dr. Van Der Kraak mentioned that EPA scientists author papers in the latest journals of endocrinology, reproduction, and biology, but that they are not necessarily at the forefront of the newest or emerging approaches for endocrine mechanisms. Dr. Safe agreed that EPA's strengths are in toxicology and risk assessment. Dr. Lucier and others on the Subcommittee agreed that

EPA's strengths should be in applying basic information to its mission not necessarily generating new information. Dr. Safe agreed that in-house basic research, such as identification of new fish progesterone receptors, might not be appropriate for EPA. They should fund this research, although they cannot and should not perform it themselves.

The Subcommittee members next discussed the program review process and identified suggestions for improving the process. Dr. Lucier did not like preparing a draft review prior to the face-to-face meeting; he prefers to listen to the presentations and then prepare a draft review report. He recommended moving the 3-hour working session held Monday afternoon to Tuesday so that the presentations could be moved to an earlier stage of the review process. Dr. Harding asked members if some of the presentations could have been condensed and held earlier. The Subcommittee members thought that 2.5 days was too long for this type of review. There was a great deal of repetition and the Monday work session probably was not necessary. The posters provided useful information, but the poster discussion sessions probably could have been shortened to half an hour.

Dr. Harding noted that some of the presentations were useful for orienting members to the subject matter of the posters. Dr. Lucier responded that information concerning poster topics was available in the packet and should have been read by members before the meeting. Dr. Van Der Kraak remarked that the material was voluminous and should have been condensed. For example, the curriculum vitas (CVs) could have been shortened to focus mainly on publication records. Dr. Harding agreed that the scientists' accomplishments could have been summarized. Originally, the EDC program was asked to do a self-study, similar to an accreditation report, and prepare a report responding to the charge questions, which the Subcommittee would evaluate. They decided that, because of time constraints, they would send all of the materials to the Subcommittee. The Subcommittee should suggest that, in the future, the program perform a self-evaluation and submit that report plus some supplemental material (such as research and implementation plans and progress reports) to the Subcommittee. Dr. Harding acknowledged that this approach would require a great deal more effort from the Program Director, but the review would be more efficient.

Presentation of LTGs

Dr. Tillitt presented a report on LTG 1. The posters helped clarify issues and were very useful to the Subcommittee. The dedication and enthusiasm of the scientists in the program was noteworthy. The program design and research goals were appropriate as were the research plans to achieve the goals. The implementation plans also were well founded and provided a logical framework to the research. The MYP addressed the ability of the program to take advantage of core resources and scientific capabilities within the federal government and illustrated the capabilities of this program that are not available in other federal agencies. Defining outcomes for these programs is necessary to promote regulatory resource management outside EPA. The STAR program brings in outside expertise and sponsors research that provides important research findings applicable to EPA's mission. The science conducted under this LTG is unique and provides a foundation required for future risk assessment and risk management activities. Useful models are in development, relevant endpoints have been chosen, and the choice of chemicals to assess is timely and important to exposure issues, particularly low-dose and long-term effects. The EDC program generates a great deal of high quality data and provides a foundation for risk management and risk assessment activities.

The program has made considerable progress, including development of important information on mode of action, exposure at different life stages, multiple exposures, dose-response characteristics, effects at multiple levels of biological organization, and linkage between assessment of response and low-dose effects of EDCs. These findings are required for appropriate evaluation of risk assessment activities. Current research on different model systems is appropriate, and relevant compounds are in use, including organochlorines, industrial compounds, and pesticides. ORD faces some challenges; measures to address these challenges are appropriate, and excellent progress has been made in development of models and endpoints and in selection of classes of chemicals.

The Subcommittee members suggested including some ideas for improvement. One issue that could be raised is how the loss of STAR funds could affect the program. Another issue is that the program relies too heavily on external scientists for some areas of research, particularly avian toxicology.

Dr. Lucier presented preliminary findings concerning LTG 2. The goals and scientific questions identified in the research plan and MYP are appropriate, representative, understandable, and provide a solid framework for setting research priorities for endocrine disruptors. Even 6 or 7 years later, the research plan remains appropriate. The relevance of the work and the progress to date was impressive, but much remains to be accomplished. The enthusiasm of the investigators and the commitment and dedication to researching the difficult and controversial problems that surround the endocrine disruptor issue were notable. The poster presentations were exceptionally well done and served to consistently address potential problems raised by the reviewers after reading the written material. EPA's future success in meeting the specified goals of the program will depend on a number of factors, including funding and support from EPA management, which can sometimes be elusive. Multidisciplinary research spanning ORD and other EPA entities, extramural grants, and intra-agency collaborations with NIEHS, CDC, USGS, FDA, USDA, and others help advance the goals of the program. Continuation of the STAR program is vital to maintain a mechanism that provides EPA with a way to more efficiently evaluate new technologies and innovations for use in the risk assessment and management arenas. The annual performance goals are ambitious, but progress on the goals should in most cases continue well past the initial timeline.

Posters for LTG 2 focused primarily on issues of environmental and human exposures to actual and suspected EDCs and the spectrum of effects that might be produced from those exposures. Some overlap exists with other LTGs, and although this overlap is desirable, it is understood that the success of each of the LTGs depends on continued productive interaction among all projects conducted under the endocrine disruptor umbrella as well as related activities appropriate to human health and environmental toxicology, risk assessment, risk management, and the needs of regional offices. To date, EPA appears to have done an exceptional job in addressing these issues with the EDC program.

In responding to charge question 1, which concerns program design, in the case of environmental releases and ecological effects EPA has taken two approaches: (1) study of chemicals with known EDC activity, and (2) evaluation of endocrine activity found in emissions and releases from different sources, followed by attempts to identify the chemicals responsible for the observed activity. Both approaches are needed, but EPA should not lose sight of determining chemical classes of interest as sources of EDCs; the report will mention some ways the Agency can do this. Priority setting for chemical classes and evaluation of their human and ecological effects should take into account newer methodologies that are capable of detecting a wide range

of endocrine active compounds. Research is ongoing to evaluate the potency of several chemical classes and the ability to test and compare chemicals for endocrine activity and potency; this research relies on adequately characterized experimental models, and many of the models required for mammalian, invertebrate, fish, and avian species appear to be developed or under development. As the models are characterized and evaluated, it will be worth developing a consensus on the utilization of these models to determine potencies for a wider range of chemicals. Current efforts using samples from the Ohio River and surface waters in California are tractable and address specific concerns. EPA also needs to determine whether the EDC program can systematically evaluate, in collaboration with FDA, the release of pharmaceutical compounds into the environment. EPA should strive to develop models that permit evaluation across multiple levels of biological organization, because such an effort is essential for a systems biology approach central to computational toxicology and for reducing uncertainties in risk assessment.

Several sources of environmental release of EDCs are under evaluation, including CAFOs, wastewater treatment, combustion processes, and paper pulp mills. These projects are well designed and should produce important data. The CAFOs studies would benefit from collaborations with state entities working on new technologies designed to minimize environmental discharges. Human health studies, including the Children's Exposure Program and the National Children's Study, represent an interagency series of large epidemiologic studies of known endocrine-disrupting agents that address reproductive and developmental effects as well as cancer. EPA is encouraged to continue these kinds of interagency activities and use the results of the exposure studies to set priorities for future epidemiologic studies so that the same substances are not tested repeatedly. EPA also is encouraged to collaborate with NIH and other agencies to ensure that appropriate markers of genetic predisposition are included in future epidemiologic studies for the purpose of identifying sensitive subpopulations.

Concerning program relevance, chemicals that have been selected for the testing and calibration of models for endocrine dysfunction represent important classes of EDCs based on known or potential exposures. The proposed and ongoing human and wildlife studies are highly relevant to EPA's mission and will be critical to future decision-making and regulatory measures for EDCs. OPPTS and the regional offices presented convincing evidence of relevance. The studies appear to be well connected to risk assessment and management needs and are addressing local problems. Results will clarify which classes of EDCs might adversely affect human health and the environment and thereby facilitate identification of sources and eliminate or reduce their release.

Good progress has been made both in intramural and extramural projects, which appear to be complimentary to one another. Several highly relevant studies are underway on potentially adverse effects of various chemicals (a list can be included in the written report); some of these compounds do not directly activate the endocrine system, but they do modulate endocrine pathways and work through other endocrine mechanisms. The adverse health effects of these compounds are hormonally mediated. All the projects presented here are making reasonable progress, although it might be difficult to meet the designated timelines in all cases. The Children's Health Initiative and interagency epidemiologic studies will take time to reach fruition, and it will be important to carefully review progress to determine when and how to take advantage of new methodologies and fields of study, such as gene arrays, proteomics, and metabolomics. The Subcommittee members were pleased with the attention given to the "omics" technologies to date and the efforts to incorporate the "omics" work performed by other

agencies into EPA's mission. EPA also will need to make decisions about when to end projects once goals have been achieved.

Dr. Van Der Kraak presented the Subcommittee's preliminary thoughts regarding LTG 3. EPA's screening and testing program was established to comply with the FQPA and SDWA. Both acts established screening programs for estrogenic activity or other endocrine activity that EPA deemed appropriate to evaluate. ORD has been responsive to the needs of the EDSP and has provided technical expertise to the OSCP. ORD also has participated extensively with OECD and other nations, particularly Japan, to harmonize methodologies for screening and testing. EPA activities included design of screening and testing methodologies and participation in round-robin testing of new methodologies. Research encompassed *in vitro* and *in vivo* models, including both vertebrate and invertebrate species. More recently, this research has expanded to include advanced QSAR models that will assist in prioritization of chemicals for testing. The quality of science in this program is uniformly high.

The overall program design is appropriate and responsive to the needs of OSCP and the international community. ORD is definitely the federal agency that should respond to this mandate because it has the in-house expertise and the ability to attract strong partners through its extramural program. This allows EPA to quickly and thoroughly respond to the needs of the OSCP. Nevertheless, ORD faces a number of challenges. In some respects, the open-ended nature of the program is daunting; development of multiple models, the difficulty of a validation process with extended partners, the need for continued refinement of what often are viewed as established methods, and the recognition that these methods in some cases require advanced levels of training and sophistication. All of these issues make the work of ORD scientists and their partners a challenge. Although the goals established in the MYP are appropriate, there is a need to more clearly delineate milestones and set targets for transfer to OSCP. In terms of relevance, the ORD research on screening and testing is essential to EPA's mission and to the mandates given to the Agency under the FQPA and SDWA. Virtually all of the short-term goals for the first several years identified in the MYP are aligned with the recommendations of EDSTAC and with EPA's efforts to comply with the nature and timing of EPA SDWA mandates. Research support and expertise from ORD have been at the forefront of developing standardized and validated screens for endocrine disruptors.

Evaluation of program progress indicates significant advances made by ORD and its scientific partners in the development and validation of several relevant bioassays important for the screening and testing requirements delineated in LTG 3. A major concern is ensuring that these methodologies are transferable to OSCP. Given the difficulties in validating routine assays, there is concern over the ability to transfer some of the more technologically demanding assays. Throughout this process, ORD has been responsive to the needs of OSCP in providing technical guidance and developing and applying testing protocols. There is little doubt that ORD has been highly responsive in addressing key scientific questions and providing the tools needed for the development and validation of testing methodologies.

Dr. Stewart addressed EDC program resources. The EDC program has an average annual budget of $12 million, including the extramural research funded under the STAR program, which has averaged approximately $4 million per year. The EDC Program Director does not have direct access to human or financial resources to carry out the program objectives. Instead, the Director must negotiate with the Division Directors of the ORD laboratories and centers to use the time and effort of scientists with the needed expertise. Approximately 55 FTEs throughout ORD are devoted to the EDC program. From the research progress made during the past 5 years, it is

apparent that the EDC Director has been successful in convincing Division Directors to lend their scientists' time to the EDC program. It also is apparent that Division Directors have been very cooperative in participating in the EDC program. However, the fragmentation of scientists' time without compensation (e.g., the addition of a laboratory technician to either carry out the scientists' originally assigned research or to perform the research necessary for the EDC program), raises concerns about productivity (e.g., the number of manuscripts published by these scientists may be negatively impacted by participation in the EDC program). The situation is complicated further by the FTE ceiling or hiring freeze currently in place throughout ORD. The hiring freeze prevents the addition of needed manpower to the affected laboratories. It is evident that insufficient resources are dedicated to the EDC program, and the mechanism used to provide those resources does not lead to maximum program efficiency.

The STAR program adds significant value to the research portfolio of the EDC program. The research sponsored by the STAR program assists in filling identified research grants, brings in research expertise that is not found among intramural scientists, and assists ORD in responding to new issues that the laboratories and centers may not be ready to address. The value of the STAR program to the EDC program was evident during this review when it was determined that 25 percent of the poster presentations selected to demonstrate the sound science of the EDC program were projects conducted by STAR grant recipients. Funding for the STAR program is declining, however, and the amount of STAR funding attributed to EDC research is variable, which does not allow maximum utility by the EDC program. The consequence of these actions is that ORD has learned to forward-fund STAR grants. This strategy gives the recipients confidence that they will receive funding for the entire period of their awards, but it significantly reduces the number of awards that can be made. In leveraging EDC program resources, the amount of research done by the EDC program has been expanded by collaboration with other agencies such as NIOSH, NCI, and NIEHS. This leveraging of resources has allowed the EDC program to get involved in areas of research, such as epidemiologic studies, for which it does not have sufficient intramural expertise and to increase the output in other research areas. Some scientists discussed informal collaborations that assist the EDC program in enhancing research productivity and meeting its goals and deadlines.

Dr. Stewart will expand this report when she receives further information about the EDC program budget. She is not entirely comfortable with the mechanism by which this program receives funding. Dr. Lucier agreed that the funding mechanism is cumbersome. Subcommittee members also discussed whether the program was under funded. Several Subcommittee members thought more budget information was needed to make a definitive assessment of funding sufficiency; however, they agreed that it would be appropriate to express concern about the funding level. Dr. Tillitt cautioned against stating that the program is under funded while simultaneously reporting that the LTGs have been met, excellent progress has been made, and productivity is high. The EDC program funding method is awkward and a more formal process is needed for allocating FTE activity to the program.

Dr. Lucier commented that the program has 55 FTEs, representing approximately 150 people, with some employees spending perhaps 20 percent of their time on EDC research, while the other 80 percent are assigned through a Division. If only 20 percent of an individual's funding, including salary, resources, and supplies, comes from the EDC program and 80 percent from the Division, this may create some conflicts. Dr. Tillitt commented that it would be more efficient to manage these issues at the center level. Dr. Stewart asked whether the report should include a statement that this structure is being reconsidered by ORD. Dr. Harding responded that she planned to include such a statement in her section of the report.

Dr. Harding expressed some concern about Dr. Stewart's statement regarding the fragmentation of scientists' time and its impact on productivity. The problem with including these statements is that scientists working with the EDC program have been very productive, although their productivity was assessed only for EDC activities and not for their other research assignments. Dr. Lucier was concerned about assigning scientists additional tasks with the expectation that they will keep up with their original tasks and produce at the same level. Dr. Harding noted that this concern relates to the issue of insufficient funding. Dr. Stewart reworded her report to read, "There is concern that the funding level may be insufficient. It also is suggested that the mechanism used to provide those resources needs to be further evaluated." The Subcommittee members agreed with this change. Dr. Van Der Kraak said he was not certain how much support for LTG 3 comes from outside of ORD. He noted that the demands on the time of the scientists supporting the EDC program seem to be high.

Dr. Harding agreed to add a sentence to the report about establishing the definition of endocrine disruptors. She will conclude the report by stating that EPA scientists are at the forefront of the field in EDC screening and testing methodologies in mammalian and ecological testing, source identification, effects on wildlife, and ecological health.

Presentation of the Subcommittee's Oral Report

On behalf of the EDC Subcommittee, Dr. Harding presented the Subcommittee's preliminary findings. She thanked all those involved for their effort and hospitality with special thanks to Dr. Francis and her team, and those who gave oral presentations and presented posters at the meeting.

The objective of the EDC program review was to assess the relevance, quality, performance, scientific leadership, and resources of the program. The Subcommittee evaluated these issues by responding to a series of charge questions that were organized specifically around program design, relevance, and progress to address key scientific questions, impact on environmental decision-making, leadership, and resources. The review was organized around the three LTGs presented in the MYP. The Subcommittee members responded to each of the charge questions relevant to program design, relevance, and progress for each of the LTGs. Charge questions 4 and 5, which focus on program resources and leadership, were evaluated separately because these topics cross-cut the entire program.

The Subcommittee received review materials prior to the meeting, including the EDC research plan, MYP, NHEERL's research implementation plan, a bibliography of publications by intramural and extramural EDC researchers, proceedings and abstracts from recent EDC workshops, abstracts of posters presented at this meeting, biographical sketches of intramural and extramural researchers, and additional reports (i.e., by the World Health Organization and EDSTAC), and a CD of the presentations from the Effective Risk Management of EDCs Workshop. These materials were distributed approximately 6 months before the review. The Subcommittee also received a synopsis of the EDC Research and Screening Program, including a logic model showing the interrelationship between the research program and screening and testing activities. At this meeting, Subcommittee members received miniaturized posters, copies of the presentations, and STAR reports.

The Subcommittee's findings from this review will be incorporated in a draft report that will be submitted to the BOSC Executive Committee in January 2005; the Executive Committee will comment on and edit the report. The final report will likely be completed later in 2005.

Dr. Harding proceeded to present a summary statement on each of the long-term goals with additional statements on program resources and leadership.

Long Term Goal 1

This goal focuses on the science underlying the effects, assessment, and management of endocrine disruptors. Information generated under this goal will help address key issues for EPA's regulatory needs, including understanding characteristics of the dose-response relationships for EDCs, particularly in the low-dose region; interspecies extrapolation for EDCs; effects of multiple exposures; management of risks associated with EDCs; and development of risk assessment approaches for EDCs. The presentations and posters for this goal were important in helping to clarify the materials presented to the Subcommittee. Both the presentations and posters provided extremely useful overviews of the research in this program. The enthusiasm, dedication, and excellence of the scientists were evident.

The goals set forth in the EDC research plan and MYP to address these issues continue to be appropriate. The research and implementation plans to achieve these goals are well-founded and provide a logical framework for achieving the goals. The program is well designed, takes advantage of existing core competencies in reproductive toxicology, mechanistic toxicology, ecotoxicology, risk assessment, and risk management methodologies to address key questions. The abilities of the scientists are unique in breadth, depth, and scope within the Federal Government. No other federal agency is equipped to provide answers regarding both risk assessment and risk management of EDCs.

The program has relied on the STAR program to supplement its intramural research and to provide expertise to achieve the outcomes. STAR grant recipients have provided important findings related to interspecies differences in steroid receptors, avian toxicology, avian and invertebrate models for EDC evaluation, and the effects of multiple EDC exposure. The program also utilized the skills and abilities of scientists from other federal agencies to complement expertise in these research areas. Programs such as the STAR program are essential to continue to meet EDC program goals.

With regard to program relevance, the science conducted under LTG 1 is unique and provides the foundation required for future risk assessment and risk management activities required by EPA. Important models are being developed and characterized, the choice of endpoints is relevant for the risk assessment process, and choices of chemicals are timely, important, and relevant to exposure. Key issues such as low-dose effects and latent effects are being addressed in a rigorous manner. Large amounts of high-quality data are being generated under this LTG, and these data will provide the foundation for environmental risk assessment and risk management of EDCs.

Relative to progress, the EDC program has developed important and relevant information on mode of action, interspecies differences, multiple chemical exposures, critical life stages, dose-response characteristics, effects at multiple levels of biological organization, linkages among assessment endpoints, and low-dose effects of EDCs. All of these findings are required for the appropriate evaluation and risk assessment of EDCs. Work on development of models such as

mammalian, fish, amphibian, and avian is ongoing and the endpoints are appropriate to help identify and evaluate uncertainties for risk assessment of EDCs. Model compounds include traditional organochlorine pesticides, industrial compounds, positive controls such as estrogens and androgens, currently used pesticides (such as atrazine), and thyroid-active agents.

The challenges faced by ORD to address the issues of multiple EDC exposures, latent effects, interspecies extrapolation, and dose-response characterization are significant, yet progress has been excellent. Researchers in the program have methodically evaluated a number of relevant models and endpoints as well as relevant chemical classes. Moreover, the models related to fish reproduction, amphibian development, and avian reproduction have provided the foundation for testing and evaluation for EDCs in future years. Careful consideration must be paid to progress under risk management issues to meet the schedules provided in the MYP.

Long Term Goal 2

The Subcommittee examined LTG 2 in relation to the charge questions on program design, relevance, and progress. The goals and science questions in the research plan and MYP are appropriate and represent an understandable and solid framework for setting research priorities for EDCs. In general, the Subcommittee was impressed with the quality and relevance of the research and the progress to date, although it is recognized that much remains to be done. The Subcommittee also was impressed with the enthusiasm of the investigators and their dedication to researching the difficult and controversial problems that surround the issues of EDCs. The poster presentations were well done and served to consistently address potential problems raised by the reviewers after they had read the written material. EPA's future success in meeting the specified goals of the program will depend on a number of factors including continued funding, support from EPA management, multidisciplinary intramural research spanning ORD and other EPA entities, extramural grants, and interagency collaborations with NIEHS, CDC, USGS, FDA, and other agencies. Continuation of the STAR program is vital as it provides a mechanism for EPA to more effectively evaluate new technologies and innovations for use in the risk assessment and risk management areas.

The Agency's annual program goal is highly ambitious and should be reviewed at a time when significant progress should be evident. The program goals should, in most cases, continue well past the initial timeline. The presentations and posters presented under LTG 2 represent primarily issues of human and environmental exposures to actual and suspected EDCs and the spectrum of effects that might be produced by these exposures. There is obvious overlap with the other LTGs, which is desirable if it is understood that the success of each of the LTGs is dependent on: (1) continued productive interactions among the projects covered under the EDC umbrella as well as related activities in programs on human health, occupational toxicology, risk assessment, risk management; and (2) support of regional needs. The Subcommittee members believe that EPA has done an exceptional job with the EDC program.

With regard to program design, the program currently studies known EDC activity and evaluates the endocrine activities of emissions and releases from different sources followed by attempts to identify the chemicals responsible for the observed activity. Both approaches are needed; EPA should not put aside the goal of determining chemical classes of interest and the sources of EDCs. The process for chemical selection under the EDC program should take advantage of the High Production Volume (HPV) Challenge Program, other EPA activities, and information obtained from FDA, CDC, NIOSH, and other relevant programs. Priority setting for chemical classes evaluated for human and ecological effects should take into account newer methodology

capable of detecting a wide range of endocrine-active compounds, including dietary phytoestrogens. Ongoing research is evaluating the potencies of several chemical classes. The ability to test and compare chemicals for their endocrine potencies relies on adequate characterization of experimental models. Many of the models required for mammalian, fish, invertebrate, and avian species appear to be developed or under development. As the models are characterized and evaluated, it will become important for EPA to fund utilization of these models to determine potencies of a wider range of chemicals. Current efforts using samples from the Ohio River and surface water in California are tractable and address specific concerns. EPA needs to determine if the EDC program should systematically evaluate, in collaboration with FDA, release of pharmaceutical compounds into the environment. Simple models of effects often are needed, but EPA should strive to develop models that permit evaluation across multiple levels of biological organization. Such an effort is essential for a systems biology approach and development of biologically based models that reduce uncertainties in risk assessment.

Several sources of environmental releases of EDCs are being evaluated including CAFOs, wastewater treatment, combustion processes, and pulp and paper mills. These projects are well designed and should produce important data. The CAFOs studies will benefit from collaboration with state entities working on new technologies designed to minimize environmental discharges. The human health studies included the Children's Exposure Program, National Children's Study, and a series of epidemiological studies of known endocrine disrupting agents. These are large studies that assess reproductive and developmental effects as well as cancer. EPA is encouraged to continue these types of interagency activities and use the results of the exposure studies to set priorities for future epidemiological studies, so the same substances are not tested repeatedly. EPA also is encouraged to collaborate with NIH and other agencies to ensure that appropriate markers of genetic predisposition are included in epidemiology studies for the purpose of identifying sensitive subpopulations.

The chemicals selected for testing and calibration of models for endocrine disruptors represent important classes of EDCs based on known or potential exposures. Proposed and ongoing human and wildlife studies are highly relevant to EPA's mission and will be critical to future decision-making and regulatory measures for EDCs. The studies appear to be well connected to risk assessment and risk management needs and are addressing local problems identified by the regional offices. Results will clarify which classes of EDCs may adversely effect human health and the environment and thereby facilitate identification of sources and eliminate or reduce their release.

Good progress has been made in both the intramural and extramural projects, and they appear to be complementary to one another. Several highly relevant studies are underway on the potential adverse effects of various classes of chemicals on human and ecological systems. These studies include evaluations of PCBs, polybrominated diphenyls, pesticides, dioxin-like compounds, synthetic and steroidal estrogens and androgens, anti-androgens, thyroid-active agents, phthalates, and polybrominated diphenyl ethers. Although some of these compounds do not directly activate hormonal systems, they modulate hormone pathways through other mechanisms and their adverse health effects are hormonally mediated. Reasonable progress is being made on the projects presented during the review, but it may be difficult to meet the designated timelines in all cases. The Children's Health Initiative and the interagency epidemiological studies will take time to reach fruition. It will be important for EPA to carefully review progress to determine when and how to take advantage of new methodologies and innovations, such as gene arrays, proteomics, and metabolomics. The Subcommittee members were pleased with the attention given to the "omics" technologies to date and the efforts to incorporate the "omics"

work performed by other agencies into EPA's mission. The Agency also will need to make decisions about when to end projects once goals have been achieved.

Long Term Goal 3

EPA's screening and testing program was established to comply with the FQPA and SDWA, both of which called for a screening program for estrogenic activity and other endocrine activity that EPA deemed appropriate to evaluate. ORD has been highly responsive to EDSP needs and provided technical expertise to OSCP. ORD also has participated extensively with the OECD and other nations, notably Japan, in the harmonization of methodologies for screening and testing methods. EPA activities included design of screening and testing methodologies and participation in round-robin testing of new methodologies. The research has encompassed *in vitro* and *in vivo* models, including both vertebrate and invertebrate species. More recently, this research has expanded to include advanced QSAR models that will assist in prioritization of chemicals for testing. The quality of science in this program is uniformly high.

The overall design of the program is appropriate. It is responsive to the needs of the OSCP and the international community. There is no question that ORD is the federal organization that should be responding to this mandate. It has the in-house expertise and the ability to attract strong partners through extramural programs. EPA has been able to respond quickly and thoroughly to the needs of the OSCP. Nevertheless, there are a number of challenges that face ORD. In some respects, the open-ended nature of the program is daunting. The development of multiple models, the difficulty of the validation process with external partners, the need for continued refinement of what often are viewed as established methods, and the recognition that these methods in some cases require an advanced level of training and sophistication makes the work by ORD scientists and their partners a challenge. Although the goals established in the MYP are appropriate, there is a need to more clearly delineate milestones and set targets for transfer to OSCP.

Pertaining to program relevance, ORD research on screening and testing is essential to EPA's mission and the mandates given to EPA under the FQPA and SDWA. Virtually all of the short-term goals identified in the MYP are aligned with the recommendations of EDSTAC and EPA's efforts to comply with nature and timing of the FQPA and SDWA mandates. Research support and expertise from ORD has been at the forefront of developing, standardizing, and validating screens for EDCs.

There has been significant progress on the part of ORD and its scientific partners in the development and validation of several relevant bioassays important for the screening and testing requirements of LTG 3. A major concern is ensuring that these methodologies are transferable to OSCP. Given the difficulties of validating routine assays, there is concern over the ability to transfer some of the more technologically demanding assays. Throughout this process, ORD has been highly responsive to the needs of OSCP in providing technical guidance for the development of revised testing protocols. There is little doubt that ORD has been highly responsive in addressing key scientific questions and providing the tools that can be applied to impact environmental decision-making.

Program Resources

The EDC program has an average annual budget of $12 million, including the extramural research funded under the STAR program, which has averaged $4 million per year. The EDC

Program Director does not have direct access to human or financial resources to carry out the program's objectives. Instead, the Director must negotiate with the Division Directors at the laboratories and centers to use the time and effort of ORD scientists needed for EDC program research activities. There are approximately 55 FTEs throughout ORD devoted to the EDC program.

From the progress made in the past 5 years, it is apparent that the EDC Program Director has been successful in convincing Division Directors to lend scientists' time to the EDC program. It also is apparent that the Divisions have been very cooperative in participating in the EDC program. However, the fragmentation of scientists' time without compensation (e.g., the addition of a laboratory technician to either carry out the scientist's originally assigned research or to perform the research necessary for the EDC program), raises concerns about productivity (e.g., the number of manuscripts published by these scientists may be negatively impacted by participation in the EDC program). The situation is complicated further by the FTE ceiling or hiring freeze currently in place throughout ORD. The hiring freeze prevents the addition of needed manpower to the affected laboratories. There is concern that the funding levels may be insufficient. It also is suggested that the mechanism used to provide EDC resources might need to be re-evaluated.

The STAR program adds significant value to the research portfolio of the EDC program. The research sponsored by the STAR program assists in filling identified research gaps, bringing in research expertise that is not found among intramural scientists, and enabling ORD to respond to new issues that the laboratories and centers may not be able to readily address. The value of the STAR program to the EDC program was evident during this review when it was determined that 25 percent of poster presentations selected to demonstrate the sound science of the EDC program were from STAR grant recipients. Funding for the STAR program is variable, sometimes is not funded at a level that allows maximum utility by the EDC program. This has lead ORD to forward-fund STAR research projects to allow the funded STAR recipients to be confident in receiving funding for the entire period of their award. This practice, however, significantly reduces the number of awards that can be made by ORD.

The amount of research performed by the EDC program scientists is expanded by collaboration with other federal agencies such as NIOSH, NIEHS, and NCI. Leveraging of resources has allowed the EDC program to become involved in areas of research, such as epidemiological studies, for which it does not have the expertise, and to increase output in other research areas. Informal collaborations are used to enhance research protocols, such as discussions between scientists at meetings on problems and their possible solutions, and to assist the EDC program in meeting its goals and deadlines.

Program Leadership

Dr. Reiter serves as the executive lead for the Endocrine Disruptors Research Program and is also the Director of NHEERL. As the lead senior administrator, he does not attend to the day-to-day issues involved with managing the program, but he does follow the program's progress and serves as a resource for the Program Director when issues arise. Dr. Reiter has been the executive lead since the inception of the program in 1995. Dr. Francis is extremely effective as the National Program Director and has done an outstanding job of providing the leadership necessary for this integrated program to thrive. Her FTE and institutional support comes from NCER and her role is to oversee the planning and execution of intramural and extramural research programs. Dr. Francis works closely with Dr. Reiter on EDC issues and reports to the

NCER Director. Under the current organizational arrangement for the National Program Director, Dr. Francis has the responsibility for program oversight, but does not have budgetary authority. A new organizational structure has been proposed and presented to the BOSC Executive Committee at a meeting held earlier in 2004, in which the National Program Director would be awarded stature comparable to the Laboratory and Center Directors. Under this new organizational structure, National Program Directors would report to the Deputy Assistant Administrator for Science and Deputy Assistant Administrator for Management. This new reporting structure might provide more management and budgetary authority to the EDC Program Director. This may be preferable to the current model in which the EDC Program Director must negotiate with various Center and Laboratory Directors for scientist FTEs to work on the EDC program.

The EDC program is unique in that no other federal agency has a comparable program. The program is not just an umbrella for a series of EDC projects but is fully integrated across all ORD's laboratories and centers with the exception of the National Homeland Security Research Center. In addition, research partners from academia, other federal agencies, and industry, participate in the program and contribute to a diverse set of talents to address various research questions. The program is nationally and internationally recognized and its multidisciplinary research in both human health and wildlife cuts across the risk assessment and risk management paradigm.

The Subcommittee recommended that EPA take the lead in establishing a definition of endocrine disruptors that is consistent and meets program needs. There is ample evidence documenting the leadership of EDC scientists both within the Agency and outside EPA. These scientists serve on national and international workgroups (e.g., providing the lead in various aspects of dioxin assessment and serving as chairs on numerous steering committees). EDC program scientists are highly sought out as consultants to EPA regional and program offices, other federal agencies, and the broader scientific community. EDC scientists also provide leadership for national and international efforts, including organizing national and international conferences. They are invited to speak, chair sessions, chair research symposia, for international conferences, and they serve on scientific review panels for other federal agencies and universities, and chair a number of interagency working groups.

EDC scientists also have been recognized for their leadership in the field as elected officers and members of professional societies. Scientists have served as reviewers on an impressive number (well over 100) of peer-reviewed journals. They have impressive CVs and have authored significant publications in top-tier journals—strong indicators of both the quality of their research and the respect of their professional peers. EDC scientists have been successful in obtaining additional funding from other federal agencies, private industry, and research foundations. They serve as adjunct professors, research fellows, fellows in academia, and as Branch Chiefs, Division Directors, and Program Directors. EDC scientists are recipients of numerous scientific and technical achievement awards, commendable service awards, and publication awards. This group of highly esteemed scientists is at the forefront of research in EDC screening and testing methodologies, mammalian and ecological testing, source identification, and risk management related to EDCs and is a valuable resource for the EDC program.

Action Items

The following action items were identified during the course of the meeting:

- ✧ Dr. Francis will send to the Subcommittee members IRIS assessments and additional budget information on the EDC program by early January.

- ✧ Dr. Lucier requested a 1- to 2-page summary of ongoing research within EPA addressing efforts to examine inter-individual variation and genetic susceptibility relevant to the EDC program.

- ✧ Dr. Francis offered to send the Subcommittee members a summary of human toxicology work sponsored by the EDC program.

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